Exhibit D

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION — MDL NO. 2327

THIS DOCUMENT RELATES TO:

WAVE 1 TVT-O CASES

DEFENDANT ETHICON'S EXPERT REPORT OF TIMOTHY A. ULATOWSKI, M.S.

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I. Qualifications

I am a consultant on matters concerning medical device regulations, policies, and procedures administered by the Food and Drug Administration (FDA) and related industry standards and best practices. I operate a registered business in the State of Virginia and the County of Fairfax, Virginia under the name Ulatowski Consulting, LLC.

I was awarded a Bachelor of Science degree in 1974 with a major in Microbiology from the Pennsylvania State University. In 1987 I was awarded a Master of Science degree in Physiology/Emphasis in Biomedical Engineering from Georgetown University, School of Medicine, in a collaborative program with Catholic University, Department of Engineering. I have additional college credits in computer science from the University of Maryland and Charles County Community College.

I was an employee of the Food and Drug Administration (FDA) from November 1974 until January 2011. During my 36 plus years of employment with FDA I held increasingly responsible positions, first for 7 years in what is now known as the Center for Drug Evaluation and Research (CDER), and the remaining years in the Center for Devices and Radiological Health (CDRH). CDRH is responsible for evaluating submissions for new medical devices, evaluating medical device clinical investigations, ensuring compliance with medical device laws and regulations administered by the FDA, conducting postmarket vigilance of marketed devices, and conducting research on medical devices.

From 1974 until 1978 I held the position of Microbiologist in the National Center for Antibiotic Analysis in CDER where I conducted laboratory analyses on antibiotics for regulatory certification purposes. From 1978 until 1980 I held the position of Consumer Safety Officer (CSO) in the Office of New Drug Evaluation (ONDE) in CDER. While at ONDE I was a product manager for the Anti-inflammatory Drugs Group and I also contributed to the Oncology and Radiopharmaceutical Drugs Groups. I was the Executive Secretary for the Arthritis Advisory Committee and managed the flow of work and outputs concerning investigational new drug applications (INDs) and New Drug Applications (NDAs). I also was the division lead on major issues such as the Drug Efficacy Study Implementation (DESI) program and the Radiopharmaceutical Drug Research Committee program. In this capacity I became thoroughly familiar with drug regulations, policies, and procedures as well as the related industry standards and best practices.

In 1980 I joined the Office of New Device Evaluation (NDE), Program Management Group, in the Bureau of Medical Devices (BMD) as a CSO. BMD was soon reorganized and joined with the Bureau of Radiological Health to form CDRH. NDE was renamed the Office of Device Evaluation (ODE).

In my first position in CDRH I was assigned to the Investigational Device Staff and was responsible for formulating policies and procedures to implement the new Investigational Device Exemptions regulation, 21 CFR Part 812, and other new human subject protection regulations dealing with informed consent and institutional review boards, 21 CFR Parts 50 and 56. I evaluated Investigational Device Exemption applications (IDEs) including protocols for clinical studies. I also evaluated and quality controlled the IDE review work of all the divisions in ODE.

In 1988 I was promoted to the Director, IDE Staff. In that capacity I was responsible for managing and directing the IDE staff, for making final decisions on the sufficiency of IDE applications and the review of those submissions by FDA staff, and for IDE regulatory compliance in collaboration with the Office of Compliance, CDRH. In this position I was the CDRH expert on the IDE regulation, policies and procedures. I also became familiar with the industry standards and best practices related to the conduct of clinical studies on medical devices.

Later in 1988 I transferred to the position of Branch Chief, General Hospital Devices in ODE. As Branch Chief I managed and directed the branch staff, and was a primary reviewer of numerous IDE applications, Premarket Notification Submissions (510(k)s), Premarket Approval Applications, new product labeling, medical device reports (MDRs) and other types of regulatory submissions under the purview of my branch. The General Hospital Devices branch evaluated products classified by FDA under 21 CFR Part 880, General Hospital Devices. The products in this classification regulation include, for example, infusion pumps and ports, administration sets and intravascular catheters. When I assumed this position until the end of my FDA career the government classified me as a Supervisory Biomedical Engineer. In this position I was an expert in premarket submission and medical device reporting regulations, policies and procedures as well as industry standards and best practices related to bringing a new device to the market.

In 1991 I was promoted to the position of Associate Director for General Devices in ODE. The scope of my responsibilities expanded to include the premarket evaluation of surgical devices classified under 21 CFR Part 878 as well as the previously assigned general hospital products. In this capacity I had broader influence on guidance, policy and procedure development spanning the entire ODE. I formulated guidance, policies, and was directly involved in the review of many significant new products such as medical lasers and computerized medical systems. As an Associate Division Director, and earlier as a Branch Chief, I instructed ODE reviewers on the policies and procedures regarding premarket submissions. My training to staff included, for example, how to identify and assess predicates and reference device information contained in a 510(k), how to assess technological characteristics and performance data.

In 1996 I was promoted to the Director, Division of Dental, Infection Control and General Hospital Devices in ODE. In this position I assumed responsibility for more product areas and all the premarket regulatory activities associated with those product areas. For example, during the course of my tenure as an ODE division director, I assumed responsibility for anesthesiology devices. During my tenure with FDA I reviewed and made agency decisions on thousands of 510(k)s and dozens of PMAs.

During my tenure at FDA I also participated as a member on FDA committees, national and international standards committees, and the Global Harmonization Task Force (GHTF).[1] The GHTF created guidance concerning industry standards and best practices related to the life cycle of medical devices and in vitro diagnostics. I was Co-Chair of the FDA committee that created the existing standards program in CDRH. The CDRH standards program evaluates national and international

[1] The Global Harmonization Task Force has transitioned to the International Medical Device Regulators Forum, www.imdrf.org.

standards to determine if FDA should recognize and utilize them as means to support product development and premarket submissions. During my tenure I also wrote the first FDA guidance documents on infusion pumps and accessories, infusion ports, sterilizers, chemical germicides, and guidance on labeling of devices intended for reuse. I was a member of the Association for the Advancement of Medical Instrumentation (AAMI) and International Standards Organization (ISO) sterilization standards committees.

In 2003 I was promoted to Director, Office of Compliance, CDRH. As the Office of Compliance Director I supervised a large staff that was responsible for ensuring industry and human subject research compliance with the medical device, radiological health, and human subject protection laws and regulations administered by FDA. I had many duties including, for example, directing inspections of medical device manufacturing facilities and clinical research facilities, evaluating Quality System and MDR-related inspection reports and taking regulatory action based on those reports, classifying recall actions, creating risk management strategies, evaluating advertising, labeling and promotional literature, leading the FDA Device Field Committee,[2] and directing responses to violations of import/export and registration laws and rules. In this position I was an expert in FDA law and regulations concerning medical devices as well as related industry standards and best practices.

I transitioned to the position of Senior Advisor for Enforcement in October 2010 in anticipation of my retirement and to allow an orderly succession of leadership. During the last four months of my FDA career I led a team formulating strategies in advance of Congressional user fee reauthorization deliberations and I provided expert advice to senior FDA leadership on premarket and compliance programs. The Commissioner awarded me for my work on user fee legislation.

During my employment with FDA I received virtually every type of award FDA can bestow including the Distinguished Career Service Award, Award of Merit, Commendable Service Awards, and numerous other individual and group awards. I maintained my management and regulatory expertise during the course of my career by attending numerous professional meetings, courses and seminars. I was frequently an invited speaker or major participant at regulatory and professional conferences here and abroad such as those held by the Food and Drug Law Institute, Regulatory Affairs Professional Society, Pharmaceutical Research and Manufacturers of America, and the American Society for Quality. In 2008 Medical Device and Diagnostic Industry News named me to their "100 Notable People" in the medical device industry. I continue to remain current on FDA policies and procedures and on industry standards and best practices.

I am currently an independent consultant. I work on premarket submissions, postmarket surveillance activities, labeling, promotion and advertising, and quality system issues for industry clients. I advise medical device and drug manufacturers on compliance matters, and provide expert testimony on FDA regulations, industry standards and best practices in litigation. I continue to be an invited speaker at professional and industry meetings. At the request of the Department of Commerce, and on FDA's referral of me to them, I trained international

[2] The Device Field Committee members include chief inspectors, senior compliance managers, and other senior FDA officers.

regulators on medical device premarket and postmarket regulatory policies and procedures and on related industry standards and best practices in October and November 2013 and again in March and May of 2014. I am scheduled to provide training to Asian regulators on behalf of the Department of Commerce and USAID in 2015.

A copy of my curriculum vitae is attached as Appendix A.

NDA Partners LLC bills for my time on this litigation at a rate of $500/hr.

I relied on my 40 plus years of training, knowledge and utilization of the FDA medical device regulations, policies, review procedures and practices as well as my knowledge and application of related industry standards and best practices in forming my opinions expressed in this report. The list of materials that I considered in forming my opinions is attached as Appendix C. I reviewed and assessed the documents in the same manner as I did while working at FDA and now as a medical device consultant. I did not rely on any commercial confidential or trade secret information obtained during the course of my employment with FDA in forming my opinions.

II. FDA's Mission, Statutory, Regulatory Provisions and Industry Standards and Best Practices Relevant to the Subject Litigation

FDA is a consumer protection agency that has roots stretching back to the turn of the last century. Its statutory authority is derived from the Federal Food, Drug, and Cosmetic Act (the act) (21 USC 301 et seq.)[3] and other acts that have been amended from time to time. Regulations implementing the statutory provisions are published in Title 21, Code of Federal Regulations (21 CFR). The first medical device amendments to the act were enacted on May 28, 1976 and there have been additional amendments in the intervening years.[4]

FDA regulates medical devices. Tension Free Vaginal Tape (TVT) is a medical device. A medical device is defined under 21 USC §321(h) as:

> *"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is (1) recognized in the National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals, or (3) intended to affect the structure or function of the body in man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependant upon being metabolized for the achievement of its primary intended purposes."*

FDA regulates the entire life cycle of medical devices. For example,

[3] References to the act are stated according to United States Code.
[4] Amendments to the act, http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/default.htm.

FDA evaluates investigational studies for new products before the studies commence,[5] it inspects manufacturing facilities,[6] it evaluates marketing applications, and it monitors the safety and effectiveness of devices during the entire course of their use. FDA regulations govern each of these activities and FDA makes available related guidance documents to inform industry, FDA staff and the public of means to address regulatory requirements.

Industry standards and best practices supplement FDA law and regulations as guides to assist in bringing devices to the market, in the manufacturing of devices, and monitoring devices in the marketplace.

A. FDA's Medical Device Program

CDRH is the primary organization within FDA that regulates medical devices. Other FDA Centers also have authority to regulate medical devices, primarily those that are a constituent of a combination product. Combination products are therapeutic or diagnostic products that consist of more than one regulated article, e.g., drug/device, and biological/device. Each combination product is regulated by the Center given primary jurisdiction for the specific combination product.

CDRH has over 1000 employees and is organized at into offices. For example, ODE is responsible for review of new devices, except for in-vitro diagnostics and radiologic products, the Office of Compliance (OC) is responsible for compliance and enforcement activities and the Office of Surveillance and Biometrics (OSB) is primarily responsible for evaluating medical device reports (MDRs), conducting epidemiology activities, and statistical reviews.

Information from each office within CDRH is integrated by computer systems available for all FDA employees to access and use in the course of performing their jobs. For example, a compliance officer in OC can easily access MDRs, inspection records, and premarket records for specific companies and devices. CDRH leverages the resources of the Office of the Associate Commissioner for Regulatory Affairs, the organizational home of FDA's inspectors. CDRH uses special government employees like nongovernment experts in the fields of medicine, engineering and statistics, and third parties to assist in premarket and compliance activities.

CDRH obtains information on medical devices for review and analysis by many means. For example, it receives required submissions according to regulations, it proactively collects information and evidence during inspections, it uses public sources of information, and increasingly it relies on regulatory bodies in other countries to provide information on imported FDA-regulated products. FDA has extensive test facilities and conducts laboratory and engineering analyses on regulated products for compliance, premarket, and postmarket surveillance purposes.

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[5] FDA does not approve "non-significant risk" devices before studies commence. This evaluation and approval is delegated to institutional review boards (21 CFR Part 56).

[6] FDA has authority to inspect all facilities subject to inspection, e.g., all places related to quality system and medical device reporting activities (21 U.S.C. §374).

B. Prohibited Acts, Misbranding and Adulteration and FDA Enforcement of Laws and Regulations It Administers

The Federal Food, Drug, and Cosmetic Act is a law enforcement statute. The law prohibits specific acts or the causing thereof, such as:[7]

> The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded;
>
> The adulteration or misbranding of any food, drug, device, or cosmetic in interstate commerce; and
>
> The receipt in interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.

1. Adulteration under the act

The act states that a device shall be deemed to be adulterated, in part (paraphrased):[8]

> If the methods used in, or the facilities or controls used for, its manufacture, packing, storage, or installation are not in conformity with applicable good manufacturing practices.
>
> It is a Class III device and is not the subject of a premarket approval application.

2. Misbranding under the act

The act states that a device shall be deemed to be misbranded, in part (paraphrased):[9]

> If its labeling is false or misleading in any particular.
>
> Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users, except that where any requirement of clause (1) of this paragraph, as applied to any drug or device, is not necessary for the protection of the public

[7] FDA applies regulatory procedures in determining whether a violation exists based upon the evidence it gathers, and when deciding the penalties or actions it may apply to remedy the violation. Penalties and violations are subject to the final concurrence by the court with jurisdiction. The violator is provided due process, e.g., to contest or appeal a charge of violation.

[8] 21 U.S.C. §351(h).

[9] 21 U.S.C. §352.

> health, the Secretary shall promulgate regulations exempting such drug or device from such requirement;
>
> It is dangerous to health when used in the dosage or manner or with the frequency or duration prescribed, recommended, or suggested in labeling thereof;
>
> If a notice or other information respecting it was not provided as required by section 510(k); or
>
> For which there has been a failure or refusal to give required notification or to furnish required material or information such as section 519, medical device reports.

The act also states the following regarding misbranding:[10]

> If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.

The misbranding provisions of 21 USC §§352(q) and (r) relating to advertising for restricted devices do NOT apply to TVT devices, including TVT-O, because TVT devices are not restricted devices.[11]

3. Tools Available to FDA to Enforce the Laws and Regulations It Administers

The FDA Regulatory Procedures Manual (RPM)[12] directs FDA personnel on internal procedures to be used in processing domestic and important regulatory and enforcement matters. While the RPM is intended mainly to provide guidance to FDA inspectors, investigators, and compliance officers, the document is useful to all of FDA and informative to the device industry.

The RPM describes the tools and actions FDA may take to help ensure compliance with the laws and regulations it administers. Those actions include (1) advisory, administrative, judicial and import actions, and (2) recall, emergency and other procedures. The key offices responsible

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[10] 21 USC §321(n).

[11] Devices must be designated by FDA as "restricted," either by a regulation promulgated under 21 USC §360j(e), or by a premarket approval application (PMA) approval order pursuant to 21 USC §360e(d)(1)(B)(ii)). Neither applies to TVT devices.

[12] FDA Regulatory Procedures Manual, http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176446.htm.

for working together on these medical device actions and procedures include the Office of Compliance/CDRH, the Office of the Associate Commissioner for Regulatory Affairs, and the Office of Chief Counsel. Other FDA offices contribute only as needed.

According to the RPM, "When it is consistent with the public protection responsibilities of FDA and depending on the nature of the violation, it is FDA's practice to give individuals and firms an opportunity to take voluntary and prompt corrective action before it initiates an enforcement action. **Warning and Untitled Letters**, both advisory actions, are issued to achieve voluntary compliance and to establish prior notice. The use of these letters and the prior notice policy are based on the expectation that most individuals and firms will voluntarily comply with the law."

The FDA compliance offices may exercise enforcement discretion when deciding whether to take enforcement action. Also, the RPM notes "there are instances when issuing a Warning Letter is not appropriate, and, as previously stated, a Warning Letter is not a prerequisite to taking enforcement action. Examples of situations where the agency will take enforcement action without necessarily issuing a Warning Letter include:

1. The violation reflects a history of repeated or continual conduct of a similar or substantially similar nature during which time the individual and/or firm has been notified of a similar or substantially similar violation;
2. The violation is intentional or flagrant;
3. The violation presents a reasonable possibility of injury or death;
4. The violations, under Title 18 U.S.C. 1001, are intentional and willful acts that once having occurred cannot be retracted. Also, such a felony violation does not require prior notice. Therefore, Title 18 U.S.C. 1001 violations are not suitable for inclusion in Warning Letters; and,
5. When adequate notice has been given by other means and the violations have not been corrected, or are continuing."

Relevant administrative actions include Section 305 notices (Citations), Section 305 meetings, administrative detention of devices, and civil money penalties (CMPs). **Detention and civil money penalties** are the most common actions taken. FDA may detain devices for a period of up to 30 calendar days if, during an inspection, the FDA has reason to believe the devices are adulterated or misbranded. The intent of administrative detention is to protect the public by preventing distribution or use of violative devices until FDA has had time to consider the appropriate action to take and, where appropriate, to initiate a regulatory action. The action of choice, in most cases, is a seizure. CMPs are monetary penalties that are assessed by FDA for violations of the law and regulations.

Some relevant judicial actions include seizure, injunction and prosecution. For a **seizure**, the United States of America, as Plaintiff, proceeds under the Supplemental Rules for Certain Admiralty and Maritime Claims (Supplemental Rules) by filing a Complaint for Forfeiture and obtaining a warrant for arrest of the device, directing the United States Marshal to seize (take possession or place in constructive custody of the court) the device. An **injunction** is a civil

judicial process initiated to stop or prevent violation of the law, such as to halt the flow of violative products in interstate commerce, and to correct the conditions that caused the violation to occur. FDA can refer cases to the Department of Justice for **criminal prosecution.**

As part of import operations the government may **refuse to admit** devices for import and can **detain** devices upon import. Section 801(a) of the Federal Food, Drug, and Cosmetic Act directs the Secretary of the Treasury to issue a Notice of Refusal when it appears from examination of samples, or otherwise, that an imported shipment is in violation. This Section also orders the destruction of any such shipment refused admission, unless it is exported within 90 days of the date of the notice, or within such additional time as may be permitted pursuant to such regulations. FDA may refuse to admit devices based on information, other than the results of examination of samples *that causes an article to appear to violate the Act*.

Two common additional procedures are the **regulatory meeting** and "**It has come to our attention**" letters. A Regulatory Meeting is a meeting requested by FDA management, at its discretion, to inform responsible individuals or firms about how one or more products, practices, processes, or other activities are considered to be in violation of the law. FDA is not required to hold a Regulatory Meeting and, except for a few specifically defined areas, is not required to provide any other form of notice before taking an enforcement action. An "It has come to our attention letter" may be issued by OC where a potential violation has been observed and FDA requests information to assess the activity. It is not an advisory or enforcement letter.

Advisory, enforcement or other compliance actions are generally initiated by OC[13] or the Office of the Associate Commissioner for Regulatory Affairs based upon potential violations identified by many sources, e.g., inspections, public or industry complaints, FDA surveillance of public information, or internal agency referrals. Only compliance and enforcement staff with the delegated responsibility can initiate, process or issue an enforcement or advisory action.

The Office of Compliance assesses internal agency referrals of a potential violation, e.g., a referral from ODE. The Office of Compliance's initial assessment includes, for example, a determination if the referral describes an activity that may be a violation, whether there is adequate documentation of the activity, and an analysis of the risk to the public health.

C. The Life Cycle of Medical Devices; Designing and Testing Medical Devices Prior to Marketing; Risk Management Throughout the Device Life Cycle

FDA, other global regulatory counterparts, and the device industry have characterized the development and marketing of a medical device as a life cycle. The cycle begins with the manufacturer developing a concept for a new or modified device, the cycle proceeds through design phases,

[13] The Office of In Vitro Diagnostic Devices and the Office of Surveillance and Biometrics can initiate compliance actions but the actions must be processed and approved through the Director of Compliance.

the design is transferred to manufacturing, the product is manufactured and the device is placed on the market. The cycle is complete when the device becomes obsolete or it recycles if the device is modified.

The design controls provisions of the FDA Quality System regulation, 21 CFR §820.30, provide the requirements a device manufacturer must incorporate into its design and development procedures and processes. Design controls consist of requirements for (1) design and development planning, (2) design inputs, (3) design outputs, (4) design reviews (5) verifying that design outputs meet design inputs requirements (6) validating that the finished device meets defined user needs and intended uses, and (7) transferring the design to manufacturing. Documentation of design activities is captured in the Design History File. Design changes before implementation are a managed process with the need for review and approval of changes, verifications and revalidation of the design, when needed.

The Quality System regulation characterizes these and other quality requirements as basic requirements.[14] Industry standards and best practices serve to supplement the regulations, for example, by helping to define the form and manner of recordkeeping indicated basically in regulation and the procedures and specific policies the device manufacturer will follow when monitoring its devices while they are in the marketplace.

FDA recognizes that manufacturers are constantly developing new and improved devices and bringing these devices to the market even while prior versions of the same type of device continue to be legally marketed. The prior versions of devices remain on the market until the manufacturer decides to discontinue these previously marketed versions.

There is no requirement to tell FDA, e.g., in a PMA or 510(k) notification, about next generation devices in the development pipeline. However, manufacturers' design and quality data concerning devices being developed are subject to FDA inspection.

Risk management is a life cycle process. Risk management is the systematic application of management policies, procedures, and practices to the tasks of identifying, analyzing, controlling, and monitoring risk.[15] Risk management is intended to be a framework within which experience, insight, and judgment are applied to successfully manage risk. Risk analysis, part of risk management, is required by the Quality System regulation as part of design validation.[16] FDA believes risk management is an important industry standard and best practice,

[14] 21 CFR §820.1(a).

[15] See discussion of risk management in FDA Design Control Guidance, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070627.htm. The International Standards Organization (ISO) Standard 14971:2007 is commonly utilized to develop the processes and procedures associated with risk management activities.

[16] 21 CFR §820.30(g).

and has recognized the international Risk Management standard, ISO 14971.[17]

Risk management by a manufacturer begins with the initial development of the design input requirements and assessment of risks known or anticipated at the initial stages of product design. In this way, unacceptable risks can be identified, to the degree possible, and managed earlier in the design process when changes are easier to make and less costly. Preliminary Hazard Analyses, Failure Modes and Effects Analyses (FMEAs),[18] Hazard and Operability Studies, Hazard Analyses and Critical Control Point, Fault Tree Analyses are examples of commonly used tools in the risk analysis process. These analyses are often contained in Risk Management Reports containing the risk assessment, risk control, residual risk and risk acceptability elements of the risk management process for a specific type of device.

Risk management is an iterative process. As the international risk management standard notes, the manufacturer should monitor production and post-production information for data and information that may affect their risk estimates.

Probability of event estimation, determination of probability levels and associated scores related to hazards are a part of risk analysis. ISO 14971:2007 states:[19]

> Seven approaches are commonly employed to estimate probabilities:
> -Use of relevant historical data
> -Prediction of probabilities using analytical or simulation techniques
> -Use of experimental data
> -Reliability estimates
> -Production data
> -Post-production information
> -Use of expert judgment

Severity of an event related to hazards is also a risk analysis factor. As with probability, for analysis purposes a manufacturer determines the levels of severity and how each level is defined.[20] A manufacturer assigns a score to each level.

Risk acceptability is typically displayed on a severity versus probability table with acceptable, unacceptable and as low as reasonably practicable regions defined by the manufacturer. The ISO standard states that all risks should be reduced to the lowest level practicable based on technical and economic factors.

Manufacturers often use risk priority numbers (RPN) in their risk analyses. The RPN is a value determined by multiplying scores of severity, probability, and detection. Risk reduction actions affect the

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[17] ISO 14971 FDA recognition, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/detail.cfm?standard__identification_no=30268.
[18] Device Design Safety Analyses are similar to FMEAs.
[19] ISO 14971:2007, Section D.3.2.2; Manufacturers sometimes use the probability cut points described in the standard when devising their risk procedures.
[20] ISO 14971:2007, Section D.3.3.

RPN by lowering the RPN. Manufacturers define RPN cut-off values to prioritize risks.

If a risk is not acceptable, as determined by the manufacturer, after risk reduction measures have been applied, then the manufacturer conducts a risk/benefit analysis to determine if the benefit of the device outweighs the residual risk. The ISO standard provides that "experienced and knowledgeable individuals" make the risk/benefit decision.[21] These individuals may be, for example, medical staff.

D. Classification and Regulatory Paths to the Market

1. Classification

Classification is fundamental to FDA's regulation of medical devices. The act establishes three classes of devices, Class I, II, and III.[22] The act provides mandatory regulatory controls for each class to provide reasonable assurance of safety and effectiveness for devices within each class. Class I is subject to "General Controls" including, for example, adulteration and misbranding, registration and listing, adverse event reporting, and good manufacturing practice (quality system) requirements. In addition to General Controls, Class II devices are generally subject to defined regulatory "Special Controls" that may include, for example, a specific guidance document, or an additional labeling requirement. Class III devices are subject to Premarket Approval but also must meet General Controls.

FDA, based on the recommendations of panels of experts, classified all devices on the market on May 28, 1976 into one of the three classes based upon the panels' assessments of safety and effectiveness of those devices. The devices were grouped into generic types such as "surgical mesh." The classifications for all types of devices are detailed in 21 CFR, Parts 862-892.

For specific devices not on the market on May 28, 1976 the act provides that any device intended for human use which was not introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976 is classified in class III unless the device is found by FDA to be "substantially equivalent" to a type of device (a predicate device) classified into class I or II. FDA determines whether the new device is substantially equivalent to a predicate by its review of what the act describes as a "report" submitted to FDA preceding introduction of the device into interstate commerce. This "report" is the 510(k) notification.

2. Paths to the Market

There are two main regulatory paths to the market for medical devices. One path is FDA approval of a premarket approval application (PMA) for a Class III device and the other is by FDA clearance of a premarket notification submission for a Class II device, commonly known as a 510(k) submission. Virtually all Class I devices and many Class II

[21] ISO 14971:2007, Section D.6.1.
[22] 21 USC §360c.

devices are exempt from the requirement to submit a 510(k) submission. The logical path, i.e., PMA or 510(k), for a manufacturer to consider for a new device depends mainly on whether there is an existing regulatory classification for a similar generic type of device. For example, there is a regulatory classification of Class II for the generic group "surgical mesh."[23] New TVT devices to date have all been a type of surgical mesh; therefore, the appropriate and logical path for a manufacturer to follow to obtain market clearance for a new TVT device would be to submit a 510(k) notification to FDA.

For purposes of this report on the Ethicon TVT-O, I will concentrate on the 510(k) submission path to clearance for marketing.

The act describes the form and manner of the "report", aka, 510(k) notification.[24] It provides, in part, that each person who is required to register and who proposes to begin the introduction or delivery for introduction into interstate commerce for commercial distribution of a device intended for human use shall, at least ninety days before making such introduction or delivery, "report" to FDA (in such form and manner as FDA shall by regulation prescribe) (1) the class in which the device is classified under Section 360c or if such person determines that the device is not classified under such section, a statement of that determination and the basis for such person's determination that the device is or is not so classified, and (2) action taken by such person to comply with requirements under 21 USC §360d (standards) or Section 360e (premarket approval) which are applicable to the device. These original fundamental provisions of a 510(k) "report" have been expanded, defined, and enriched in several amendments to the act after 1976.

The term "substantially equivalent", which I have noted above, is at the core of classification by means of a 510(k) submission. An amendment to 360c(i) of the act incorporated a definition of this term that FDA had previously included in guidance. According to the act, "substantially equivalent" or "substantial equivalence" means that the new device has the same intended use as the predicate device and the same technological characteristics, or if it does not have the same characteristics then information submitted demonstrates that the new device is as safe and effective as the predicate and does not raise different questions of safety and effectiveness than the predicate device. The FDA review criteria discussed below for a 510(k) submission incorporate this statutory provision and expand upon it.

According to a recent FDA guidance, safety and effectiveness is an inherent part of FDA's determination of substantial equivalence.[25] The guidance states, "The 510(k) review standard (substantial equivalence of a new device to a legally marketed (predicate) device) differs from the PMA review standard (reasonable assurance of safety and effectiveness). The 510(k) review standard is comparative, whereas the PMA standard relies on an independent demonstration of safety and

[23] 21 CFR §880.3300.
[24] 21 U.S.C. §360(k).
[25] Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)], http://www.fda.gov/downloads/medicaldevices/.../ucm284443.pdf.

effectiveness. Nonetheless, the principles of safety and effectiveness underlie the substantial equivalence determination in every 510(k) review."

3. Premarket Notification Submissions

The 510(k) regulation, 21 CFR §807.81, describes when a 510(k) is required. In part, a 510(k) is required for a device being marketed for the first time or for a marketed device that is to be significantly changed or modified in design, components, method of manufacture, or intended use.[26]

The regulation under 21 CFR §807.87 also describes information required in a 510(k). The 510(k) must include, in part: labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for its use; comparisons to other legally marketed devices; and any other information the FDA needs to determine substantial equivalence.[27] FDA's review of 510(k) data and information is rigorous and thorough.

There is ample FDA guidance pertaining to 510(k)s. Some FDA guidance applies to the submission process in general[28] while product-specific guidance, if available, provides more details on format and content for a 510(k). The details may include standards that should be applied, specific tests and outputs, and specific labeling recommendations.

Guidance is not mandatory. FDA Good Guidance Practices (GGPs) state "You (for instance a manufacturer) may choose to use an approach other than the one set forth in a guidance document. However, your alternative approach must comply with the relevant statutes and regulations."[29] GGPs also state "Although guidance documents do not legally bind FDA, they represent the agency's current thinking. Therefore, FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence."

FDA issued guidance for surgical mesh in 1999, which is the generic type of device under which vaginal slings are classified.[30] The guidance recommends that 510(k)s for surgical mesh include, in part: a summary of safety and effectiveness or a statement that such information is available upon request, specification of all material components of the device, manufacturing information, packaging information, product

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[26] Many Class I and some Class II devices are exempt from 510(k) notification requirements.
[27] "any other information" may include, for example, preclinical or clinical data, or revised labeling.
[28] 510(k) Submission Process, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm070201.htm.
[29] 21 CFR §10.115.
[30] Guidance for Industry and/or for FDA Reviewers/Staff and/or Compliance - Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073790.htm.

characterization, and labeling. The document states a final consideration that additional information may be required as technological advances continue but it does not specifically identify the need for clinical data.

There are three types of 510(k) submissions including traditional, special and abbreviated. Traditional submissions can be used under any circumstances and include all information typically required for a 510(k) submission. Abbreviated submissions may include some abbreviated information compared to a traditional submission because this submission method relies on "declarations of conformity" to FDA-recognized standards the manufacturer used when designing and/or manufacturing the device. A special 510(k) may be used when a manufacturer wishes to significantly modify one of its own legally marketed devices. These three processes are described in FDA guidance.[31]

From its review of a 510(k) submission, the FDA may determine, by order, that a 510(k) submission is substantially equivalent (SE), SE with limitations,[32] not substantially equivalent (NSE), or that additional information is needed to render a decision (AI). FDA considers a device that it finds SE by means of a 510(k) to be "cleared." A device is "approved" only by an FDA approval order for a premarket approval application.

Prior to the Safe Medical Devices Act of 1990 (SMDA)[33] manufacturers could go to market after 90 days of submission of the 510(k) unless FDA intervened beforehand by either calling the submitter to "hold" the review clock, or by issuing an Additional Information (AI) or Not Substantially Equivalent (NSE) letter. Now, FDA must issue an order for a 510(k) declaring the device equivalent before the device may be marketed.

The current language in the standard FDA Additional Information (AI) letters that "You may not market this device until…you have received a letter from FDA allowing you to do so" was included in the form AI letter after SMDA in 1990. FDA may apply enforcement discretion regarding this provision in certain cases.[34] The AI letter is also an administrative letter issued by the Office of Device Evaluation simply

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[31] The New 510(k) Paradigm: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm.

[32] Determination of Intended Use for 510(k) Devices; Guidance for CDRH Staff (Update to 98-1), http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm082162.htm.

[33] SMDA, The Safe Medical Devices Act of 1990 (P.L. 101-629), which amended the FFD&C Act (21 U.S.C. 201 et seq.), was signed into law on November 28, 1990.

[34] Two cases where enforcement discretion has been applied include (1) a device is modified after a recall and continues to be marketed and then changes to the device are submitted in a 510(k). (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080297.htm), and (2) submission of a 510(k) after a device has been marketed when FDA requests voluntary submission and ODE makes an enforcement referral to OC, e.g., a manufacturer makes a change to a device it deemed not significant but is later deemed significant by FDA.

to convey to the manufacturer the information ODE needs to complete its review. It is not an enforcement action.

FDA notes that there are "…many changes in the evolution of a device."[35] When making changes to a marketed device a manufacturer determines that a new 510(k) is needed according to regulation when:

> the device is one that the person currently has in commercial distribution or is reintroducing into commercial distribution, but that is about to be significantly changed or modified in design, components, method of manufacture, or intended use. The following constitute significant changes or modifications that require a premarket notification:
> (i) A change or modification in the device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process.
> (ii) A major change or modification in the intended use of the device.[36]

The FDA guidance document "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), January 10, 1997"[37] was developed to help assist manufacturers in deciding when a change to a device was "significant" or "major." FDA notes in the guidance "To be certain that a decision on when to submit a 510(k) is correct, one would probably need to enumerate all device types and all potential types of changes and then match each combination of device and change with a decision. Given that there are thousands of individual device types and possibly tens or hundreds of enumerable changes, this would be an impossible task. Furthermore, the resultant guidance would fill volumes, would probably be difficult to use, and would be unlikely to keep pace with an ever-changing technology."

While the guidance tries to provide general guidance on making decisions regarding changes to devices it is clear that FDA relies heavily on manufacturer compliance with the Quality System regulation as the fundamental means of ensuring device safety and effectiveness. The guidance states, "For many types of changes to a device, it may be found that a 510(k) is not necessary, and the Agency may reasonably rely on good manufacturing practices (either as implemented under the 1978 GMP or the Quality Systems regulation) to continue to assure the safety and effectiveness of the changed device. This reliance is enhanced when manufacturers document their decision-making based on their testing results or other design validation criteria." Also, manufacturers "must have a process in place to demonstrate that the manufactured device meets the change in design specifications (or the original specifications, if no change was intended). They must keep records, and these records must be made available to an FDA inspector." The guidance states, "No matter how carefully this guidance is applied, there will still be decisions in a "gray area" that manufacturers will

[35] FDA Guidance: Deciding When to Submit a 510(k) for a Change to an Existing Device.
[36] 21 CFR §807.81(3).
[37] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm.

have to make (emphasis added)."[38] Manufacturers are encouraged, but not required, to contact FDA when the proposed change is not addressed in the guidance flowcharts. In fact, in my experience it was rare that a manufacturer called my division in ODE or the Office of Compliance to request an opinion on a change to a marketed device.

It was reported in 2008 that there are more than 20,000 companies worldwide and 80,000 brands and models of devices.[39] So, based on the fact that FDA notes there are numerous changes with devices, there are probably tens of thousands of changes to devices in any given year. However, for example, there were only 3363 510(k)s submitted in 2008, and only 653 were special 510(k)s.[40] Various conclusions could be drawn from this data but it is evident that relatively few changes to marketed devices result in new 510(k) submissions.

FDA proposed a revision to the K97-1 guidance in 2011 based upon its current thinking about changes to devices. Congress rebuked FDA due to the content of the draft guidance, requiring the following extraordinary actions in the Food and Drug Safety and Innovation Act (FDSIA):[41]

> Not later than 18 months after the date of enactment of this paragraph, the Secretary shall submit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate a report regarding when a premarket notification under subsection (k) should be submitted for a modification or change to a legally marketed device. The report shall include the Secretary's interpretation of the following terms: 'could significantly affect the safety or effectiveness of the device', 'a significant change or modification in design, material, chemical composition, energy source, or manufacturing process', and 'major change or modification in the intended use of the device. The report also shall discuss possible processes for industry to use to determine whether a new submission under subsection (k) is required and shall analyze how to leverage existing quality system requirements to reduce premarket burden, facilitate continual device improvement, and provide reasonable assurance of safety and effectiveness of modified devices.

The law also states

> The Secretary shall withdraw the Food and Drug Administration draft guidance entitled 'Guidance for Industry and FDA Staff— 510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device', dated July 27, 2011, and shall not use this draft guidance as part of, or for the basis of, any premarket review or any compliance or enforcement decisions or

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[38] Ibid.
[39] Advamed. The 510(k) Process: The Key to Effective Device Regulation, 8/19/08.
[40] ODE Annual Report 2008. Special 510(k)s are meant for changes to marketed devices.
[41] http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm20027187.htm.

actions.

Congress directed FDA to keep in place the K97-1 guidance until Congress concurred with any new FDA guidance on the issue as noted above. FDA submitted a report to Congress on its intentions regarding this guidance and withdrew the draft guidance on July 17, 2012.[42,43]

The upshot of these recent mandatory statutory provisions related to modifications to marketed devices and the need to submit a new 510(k) is that Congress was telling FDA (1) there is a need for industry and FDA consensus on the definition of terms used in the 510(k) regulation related to modification of devices, suggesting even the existing K97-1 guidance and processes are unsatisfactory, (2) Congress will not tolerate a stringent or expanded interpretation of when a 510(k) is needed for a change to a device, as was the case in the withdrawn 2011 guidance, and (3) compliance with the Quality System regulation should be used as a foundation for "reasonable assurance of safety and effectiveness of modified devices.

In the recent FDSIA amendment Congress uses the terms "reasonable assurance of safety and effectiveness" related to regulation of modified 510(k) devices and not "substantial equivalence" thus further blurring the line between premarket approval and premarket notification.

4. How FDA Determined Substantial Equivalence for TVT Devices Prior to July 28, 2014

FDA premarket submission reviewers used the decision flowchart first described in a 1986 FDA guidance document when determining substantial equivalence of the TVT devices such as the Ethicon TVT-O device and when documenting their decision.[44] As noted above, the substantial equivalence decision process contained in FDA guidance was incorporated into the act.

The 1986 guidance document describes the key decision elements in determining substantial equivalence, as follows:

> *Thus, as a matter of practice, CDRH generally considers a device to be SE to a predicate device if, in comparison to the predicate device:*
>
> *the new device has the same intended use (as discussed below); and,*
>
> *the new device has the same technological characteristics, (i.e., same materials, design, energy source, etc.); or, it has new technological characteristics that could not affect safety or*

[42] Withdrawal of draft guidance, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm265274.htm.

[43] http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM387121.pdf.

[44] Guidance on the CDRH Premarket Notification Review Program 6/30/86. (K86-3), 510(k) Memorandum #K86-3: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm. This flowchart was updated in 2014.

effectiveness; or

it has new technological characteristics that could affect safety or effectiveness, and

-- there are accepted scientific methods for evaluating whether safety or effectiveness has been adversely affected as a result of the use of new technological characteristics; and

-- there are data to demonstrate that the new technological features have not diminished safety or effectiveness.

The document describes decision aspects when determining whether the new device has the same intended use as the predicate as follows:

While a new device must have the same intended use as a predicate device in order to be SE, the Center does not require that a new device be labeled with precise therapeutic or diagnostic statements identical to those that appear on predicate device labeling in order for the new device to have the same intended use. Label statements may vary. Certain elements of a predicate device's labeled indication may not be critical to its intended therapeutic, diagnostic, prosthetic, surgical, etc., use. The Center's scientific expertise enables it to exercise considerable discretion in construing intended uses in the labeling and promotional materials for predicate and new devices. Thus, a new device with the same intended use as a predicate device may have different specific indication statements, and, as long as these label indications do not introduce questions about safety or effectiveness different from those that were posed by the predicate device's intended use, the new device may be found SE.

For the purposes of determining whether or not the new device has the same intended use as a predicate device, the Center assesses any difference in label indications in terms of the safety and effectiveness questions they may raise. The Center considers such points as physiological purpose (e.g. removes water from blood, transports blood, cuts tissue), condition or disease to be treated or diagnosed, professional or lay use, parts of the body or types of tissue involved, frequency of use, etc. If a new device is determined to have the same intended use, the Center may then proceed to determine whether or not it is substantially equivalent. (Devices which do not have the same intended use cannot be substantially equivalent.)

For technological differences the guidance states:

Thus, from a scientific perspective, to determine which technological changes are consequential, the Center considers whether:

- *the new device poses the same type of questions (emphasis added) about safety or effectiveness as a predicate device.;*
- *there are accepted scientific methods for evaluating whether safety or effectiveness has been adversely affected as a result of the use of new technological characteristics; and*
- *there are data to demonstrate that new technological characteristics have not diminished safety or effectiveness*

In terms of performance data the guidance notes:

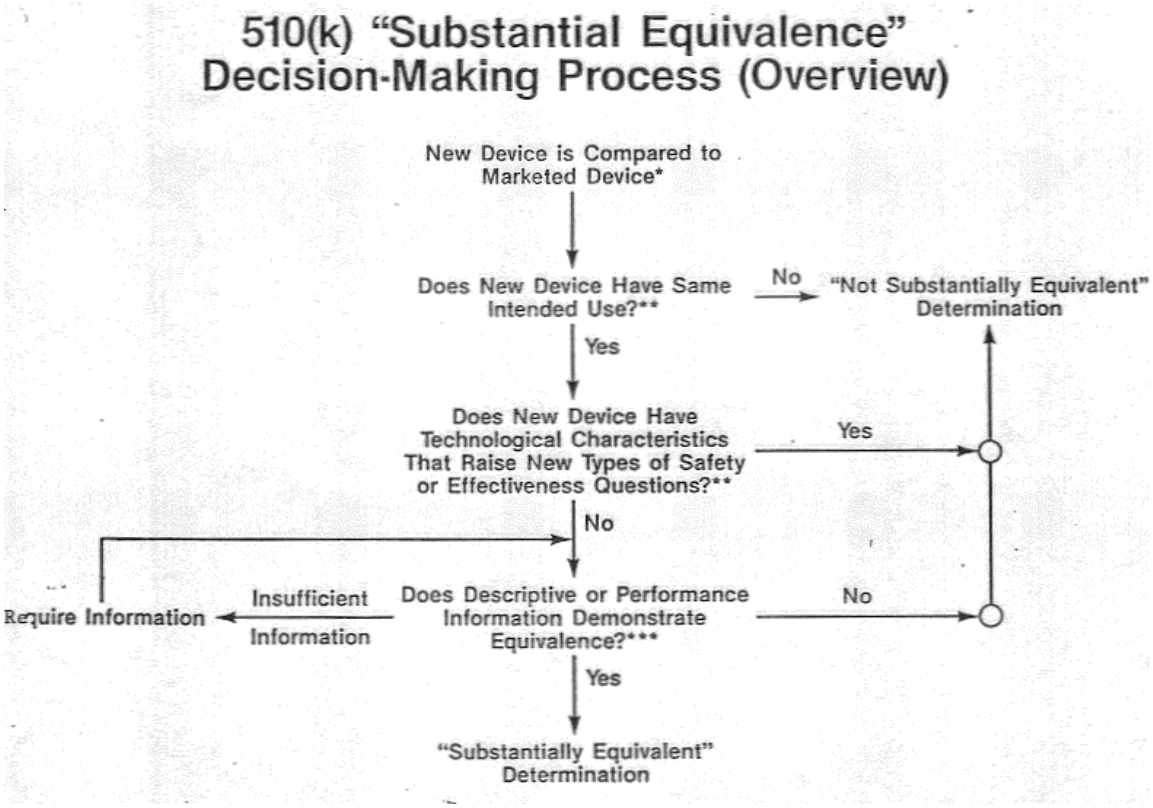
> *Typically, 510(k) provides descriptive and testing data that compares the new device to another marketed device within the type, but does not necessarily compare the new device directly to a predicate device. In these cases, the Center can rely, as necessary, on performance data appearing in previously reviewed 510(k) files, in Center classification files, or in the literature, to determine that the device is not only comparable to another marketed device within its type, but is also SE to a predicate device.*

FDA's consideration of substantial equivalence evolved over time to incorporate the consideration of a "reference device" when assessing performance data.[45] A submitter may use a reference device, which is a legally marketed device that has a different intended use or different technological characteristics that raise different questions of safety and effectiveness, to address specific scientific questions or performance characteristics for a new device. For example, a reference device may be useful as supportive evidence of the safety of a material used in a new device.

A summary version of the decision tree taken from the 1986 guidance and used by FDA and industry for the determination of substantial equivalence and documentation of the decision is as follows:[46]

[45] The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications, http://www.fda.gov/downloads/medicaldevices/.../ucm284443.pdf.

[46] An updated chart posted by FDA and used for FDA and industry documentation purposes (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM081395.pdf) has essentially the same elements, but expands the considerations regarding the need for performance data.



5. Significant Changes to 510(k)s Since 1976 Relating to the Evaluation of Safety and Effectiveness

The 510(k) submission process has evolved due to statutory, regulatory and procedural changes. The fundamental design process and the creation and maintenance is controlled by the quality system regulation The 510(k) process is a considerable hurdle to manufacturers seeking to market a new device.

The first significant change to the act after 1976 regarding 510(k)s was the Safe Medical Device Act of 1990 (SMDA).[47] SMDA increased the authority of FDA and the requirements for manufacturers, morphing Class II determinations into decisions about safety and effectiveness by requiring FDA to make decisions on the reasonable assurance of safety and efficacy of the device. The definition of "substantial equivalence" was incorporated into the act, as noted above in this report. Additionally, "Special Controls" replaced "Performance Standards" for Class II devices as noted earlier in this report. Further, a summary of safety and effectiveness was required, preproduction design controls were now regulated, FDA had to issue a 510(k) equivalence order before a device submitted under a 510(k) could be marketed, and correction and removal reports were required. Also, the relatively few 510(k)s for Class III devices had to now include a summary of adverse data relating to the safety and effectiveness of the device.

[47] The Safe Medical Devices Act of 1990 (P.L. 101-629), which amended the FFD&C Act (21 U.S.C. 201 et seq.), was signed into law on November 28, 1990.

The next change was the FDA Modernization Act of 1997.[48] FDAMA focused FDA resources on those devices presenting the most risk. FDAMA instituted "Good Guidance Practices" to strengthen the development and vetting of documents to the public. The "least burdensome" principles were also added. In a guidance document[49] FDA defined least burdensome as "a successful means of addressing a premarket issue that involves the most appropriate investment of time, effort, and resources on the part of industry and FDA."

The Medical Device User Fee Act of 2002 (MDUFMA) was enacted "in order to provide the Food and Drug Administration (FDA) with the resources necessary to better review medical devices, to enact needed regulatory reforms so that medical device manufacturers can bring their safe and effective devices to the American people at an earlier time…"[50]

As I note above, on July 28, 2014, FDA posted new guidance regarding the evaluation of substantial equivalence in premarket notifications stating the principles of safety and effectiveness underlie the determination of equivalence. FDA also posted draft guidance on benefit-risk factors to consider when determining substantial equivalence in premarket notifications.[51] It is clearly evident that the 510(k) process is and will continue to be a viable path to the determination by FDA of the reasonable assurance of safety and effectiveness for new medical devices not subject to PMAs.

E. Postmarket Surveillance, Monitoring Device Experience: Complaints, Medical Devices Reports, Corrective and Preventive Actions

Once a device is marketed manufacturers and FDA continue to monitor the device's safety and effectiveness. Three regulatory life cycle activities associated with postmarket surveillance are closely linked and describe the basic requirements of the system for receiving, assessing and taking appropriate action based on postmarket signals. These activities include complaint handling, medical device reports, and corrective and preventive actions. Industry standards and best practices play an important role in formulating the documentation, policies and procedures for these quality management activities.

As required by 21 CFR §820.198, Complaint Files, each manufacturer shall establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit. Such procedures

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[48] FDAMA, http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/default.htm.

[49] The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085994.htm.

[50] MDUFA, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109149.htm

[51] Benefit-Risk Factors to Consider When Determining Substantial Equivalence in 510(k)s, http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm282958.htm

shall ensure that the manufacturer (1) processes all complaints in a uniform and timely manner, and (2) evaluates all complaints to determine whether any complaints represent an event, which is required to be reported to FDA under part 803, Medical Device Reporting. The manufacturer is required to evaluate complaints and make investigations as needed. Any complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications shall be reviewed, evaluated, and investigated, unless such investigation has already been performed for a similar complaint and another investigation is not necessary.

The medical device reporting regulation, 21 CFR Part 803, establishes the requirements for medical device reporting of events identified in the complaint process for device user facilities, manufacturers, and importers. A manufacturer or importer must report to FDA deaths and serious injuries its device has or may have *"caused or contributed"* to and, certain device malfunctions, and the manufacturer or importer must establish and maintain adverse event files. A manufacturer must also submit specified follow-up.

The term "caused or contributed" by regulation means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of failure, improper or inadequate design, manufacture, labeling, or user error.[52]

According to FDA, "(MDR) Reports are not required when there is information that would cause a person who is qualified to make a medical judgment (e.g., a physician, risk manager, or biomedical engineer) to reach a reasonable conclusion that a device did not cause or contribute to an MDR reportable event. Information that leads to the conclusion that an event is not reportable must be retained in the MDR event files for the time periods specified in Sec. 803.18."[53] This provision is part of the MDR regulation.[54]

FDA posts MDRs on the MAUDE database.[55] FDA states on its web site, "MAUDE data is not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices."

In Subpart J of 21 CFR §820, Corrective and Preventive Action,[56] also known as CAPA, it is required that manufacturers establish and maintain procedures for implementing corrective and preventive action. The procedures shall include requirements, in part, for analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of product that do not meet a specific requirement (i.e., a nonconformity), or other quality problems.

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[52] 21 CFR §803.3.
[53] FR Notice, Vol.60, No.237 (12/11/95), comment 11.
[54] 21 CFR §803.20(c)(2).
[55] MAUDE, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM.
[56] 21 CFR §820.100.

The manufacturer must investigate the cause of nonconformities relating to product, processes, and the quality system; identify the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems; verify or validate the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device; implement and record changes in methods and procedures needed to correct and prevent identified quality problems; and ensure that information related to quality problems or nonconforming product is disseminated to those directly responsible.

So, for example, if a complaint is received concerning a death or injury then the manufacturer is obligated to assess it and determine if an investigation is warranted and whether an MDR report must be submitted. Steps may be taken to mitigate the event and/or likelihood of the event reoccurring based on reestablished CAPA procedures. Outputs of decision-making in CAPA may be a recall, labeling changes, notices to users, or other actions.

FDA inspects manufacturers to help ensure compliance with 21 CFR Parts 820 and 803, including the complaint, MDR, and CAPA processes. It uses the Quality System Inspection Technique (QSIT) guidance[57] for FDA investigators as one basis for evaluating these processes.

F. Medical Device Labeling Regulations

The term "labeling" means all labels and other written, printed or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.[58] The term "label", in part, means a display of written, printed, or graphic matter upon the immediate container of any article.[59] Labeling includes important information to the end user to enable him or her to use the product safely and effectively for the indications listed therein.

Labeling requirements for medical devices are provided in 21 CFR Part 801, Labeling. The labeling regulation describes the form and content of labeling, provisions for devices labeled for over the counter use, and specific statements for certain devices. Adequate directions for use, 21 CFR §801.5, provide labeling requirements for devices intended for lay use, i.e., over-the-counter product.

1. Content and Format of Prescription Labeling

An exemption from adequate directions for lay use is provided for prescription devices. As noted in the regulation:

> *A device which, because of any potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use is not safe except under the supervision of a practitioner licensed by law to direct the use of such device, and hence for which "adequate directions for use" cannot be prepared, shall be exempt from section 502(f)(1) of the act if*

[57] http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm.
[58] Section 201(m) of the act (21 USC §321(m)).
[59] Section 201(k) of the act (21 USC §321(k)).

all the following conditions are met:

(a) The device is:

(1)(i) In the possession of a person, or his agents or employees, regularly and lawfully engaged in the manufacture, transportation, storage, or wholesale or retail distribution of such device; or

(ii) In the possession of a practitioner, such as physicians, dentists, and veterinarians, licensed by law to use or order the use of such device; and

(2) Is to be sold only to or on the prescription or other order of such practitioner for use in the course of his professional practice.

(b) The label of the device, other than surgical instruments, bears:

(1) The statement "Caution: Federal law restricts this device to sale by or on the order of a ____", the blank to be filled with the word "physician", "dentist", "veterinarian", or with the descriptive designation of any other practitioner licensed by the law of the State in which he practices to use or order the use of the device; and

(2) The method of its application or use.

(c) Labeling on or within the package from which the device is to be dispensed bears information for use, including indications, effects, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the device can use the device safely and for the purpose for which it is intended, including all purposes for which it is advertised or represented: Provided, however, that such information may be omitted from the dispensing package if, but only if, the article is a device for which directions, hazards, warnings, and other information are commonly known to practitioners licensed by law to use the device. Upon written request, stating reasonable grounds therefore, the Commissioner will offer an opinion on a proposal to omit such information from the dispensing package under this proviso.

(d) Any labeling, as defined in section 201(m) of the act, whether or not it is on or within a package from which the device is to be dispensed, distributed by or on behalf of the manufacturer, packer, or distributor of the device, that furnishes or purports to furnish information for use of the device contains adequate information for such use, including indications, effects, routes, methods, and frequency and duration of administration and any relevant hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to employ the device can use the device safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented. This information will not be required on so-called reminder--piece labeling which calls attention to the name of the device but does not include indications or other use information.

(e) All labeling, except labels and cartons, bearing information for use of the device also bears the date of the issuance or the

date of the latest revision of such labeling.

2. Definitions of Intended Use, Indications, Contraindications, Warnings and Precautions

There are several terms identified in the FDA device labeling regulation, 21 CFR Part 801 as follows:

Intended Use: FDA labeling regulation, 21 CFR §801.4, defines the term "intended use" as follows:

> *The words intended uses or words of similar import in §§ 801.5, 801.119, and 801.122 refer to the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. The intended uses of an article may change after its manufacturer has introduced it into interstate commerce. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he received the devices, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. But if a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses to which the article is to be put.*

Indications: The term "indications" is not defined in the medical device labeling regulation, 21 CFR Part 801. In 21 CFR §814.209(b)(3)(i), Indications for Use is stated as:

> *A general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.*

Device Labeling Guidance[60] states the Indications for Use identifies the target population in a significant portion of which sufficient valid

[60] Device Labeling Guidance #G91-1 (blue book memo), http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081368.htm. This guidance is based on drug regulations and reflects FDA's "current thinking" in 1991. The device labeling regulation uses the terms any "hazards" and "side effects" while "adverse reactions" in the guidance is a term used for drugs. There are no general device regulations other than 21 CFR Part 801 describing the content requirements of labeling.

scientific evidence has demonstrated that the device as labeled will provide clinically significant results and at the same time does not present an unreasonable risk of illness or injury associated with the use of the device. As appropriate, the labeling should state that the device (trade name) is "indicated" or "intended for use"

> (1) in the treatment, mitigation, prevention or diagnosis of a recognized disease or condition or an important manifestation of a disease or condition; and/or,
> (2) in the relief or mitigation of symptoms associated with a disease or condition; and/or,
> (3) as an aid or adjunct to a mode of therapy or diagnosis.

Contraindications: As suggested in the labeling guidance this section describes situations in which the device should not be used because the risk of use clearly outweighs any possible benefit. Known hazards and not theoretical possibilities are to be listed.

Warnings: As suggested in the labeling guidance this section describes serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. Labeling should include an appropriate warning if there is reasonable evidence of an association of a serious hazard with the use of the device. A causal relationship need not have been proved.

A warning is appropriate when the device is commonly used for a disease or condition for which there is a lack of valid scientific evidence of effectiveness for that disease or condition and such usage is associated with a serious risk or hazard.

Precautions: As suggested in the labeling guidance this section includes information regarding any special care to be exercised by the practitioner and/or patient for the safe and effective use of the device.

Adverse Reactions: As suggested in the labeling guidance an adverse reaction is an undesirable effect, reasonably associated with the use of the device that may occur as part of the effect of the device or may be unpredictable in its occurrence.

According to the drug regulation-based FDA guidance this section includes all adverse reactions reasonably associated with the use of the device, including those mentioned in the "Contraindications", "Warnings" and "Precautions" sections of the labeling. The listing of the adverse reactions should be followed, if appropriate, by statements directing the reader to other sections of the labeling for additional information regarding these adverse reactions and any steps that should be taken.

3. Promotion and Advertising

The term "promotion" is not defined in the act or device regulations. Promotion is a form of advertisement by common definition.[61]

There are some rules on device advertising in the act. As noted earlier

[61] www.merriam-webster.com.

in this report, 21 USC §§352(q) and (r) provide prohibitions on restricted device advertising. However, surgical mesh such as the Ethicon TVT-O device is not a restricted device.[62] FDA has authority to find device labeling false and misleading. Misleading labeling and advertising is defined under 21 USC §321(n). There are no medical device advertising regulations as there are for drugs. Advertising regulations pertaining to drugs, 21 CFR Part 202, are unenforceable for devices.

In my experience heading the Office of Compliance for devices the characterization of device advertising as labeling is typically unsuccessful in enforcement actions when there is no physical association of the device with the advertisement, i.e., it does not accompany the device. A 70-year-old appellate court case decision referenced by FDA guidance discussed the connection between labeling and advertising.[63] However, this was a case against a drug manufacturer and the case predated drug-advertising rules. The manufacturer claimed that circulars accompanying the drug were advertising and not labeling. The printed advertising in this case accompanied the drug and, not surprisingly, was deemed to be labeling by the court.

The Federal Trade Commission has authority for advertising of devices that are not restricted devices while FDA exercises its authority over restricted device advertising.[64]

4. False and Misleading Device Labeling

A device is misbranded if its label "is false or misleading in any particular."[65] The act also states "If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual."[66] There are misbranding provisions for only restricted device advertising. Drug labeling or advertising laws and regulations cannot be applied to misbranding for devices or enforced for devices.

FDA has previously issued guidance concerning false or misleading labeling[67] but this Device Advice guidance is not an enforcement guidance issued by the Office of Compliance or FDA Office of the Chief Counsel. The Device Advice guidance is not enforceable except where it

[62] Devices have been designated by FDA as "restricted," either by regulation promulgated under 21 USC 360j(e), or by premarket approval application (PMA) approval order pursuant to 21 USC §360e(d)(1)(B)(ii).
[63] United States v. Research Laboratories, inc., 126 F.2d 42, 1942, U.S. App. LEXUS 4060.
[64] http://www.fda.gov/NewsEvents/Testimony/ucm096272.htm.
[65] 21 USC §352(a).
[66] 21 USC §321(n).
[67] Device Advice – Labeling Requirements:Misbranding.

refers to statute or regulation.

5. Patient Labeling

There is no general FDA regulatory requirement that a manufacturer must provide patient labeling for a prescription device, nor are there mandatory stipulations on the content and format of patient labeling.[68] FDA can require patient labeling for a specific device either as a condition of approval in a PMA approval order,[69] as part of a Class II device special controls guidance document,[70] or otherwise by a device-specific labeling regulation.[71] There are no such requirements for TVT devices.

Manufacturers, who are not required to provide patient labeling, as is the case for surgical mesh,[72] do so voluntarily on their own initiative in keeping with industry standards and best practices for these types of devices. Patient brochures, patient directed circulars or handouts, leaflets, videos, or information sheets intended for and made available to or provided to the patient constitute types of patient labeling.

FDA posted guidance on patient labeling in 2001.[73] The guidance describes suggested content and formatting of patient labeling. Risk/benefit information is addressed in the guidance. In regard to warnings it states, "Including too many warnings and precautions, over-warning, dilutes the strength of all of the hazard alerts. We recommend that writers use care in what is designated as a warning or precaution. Careless designation can have the same diluting effect as over-warning."

In regard to adverse effects the guidance states, "When appropriate, provide information about any adverse events. Devices whose applications are supported by clinical trials will have data about adverse events that occurred during these trials and that may be of value to the device user. Other devices may have adverse event data from other sources, e.g., published literature or experience with similar devices. The detail in and the need to include an Adverse Events section depend on the benefit of these data to the device user. For a device cleared under Premarket Notification, which was not supported by clinical studies, the Adverse Events section might include only potential adverse events and a statement of the source of the information." It is clear to me that the suggestions in the guidance

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[68] 21 CFR §801.109(d), labeling other than IFUs, can be interpreted to mean an IFU should be attached to any patient labeling.
[69] 21 CFR §814.44(e).
[70] General and Special Controls, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/default.htm#class_2.
[71] 21 CFR Part 801, Subpart H.
[72] FDA's Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh, is not a PMA requirement or a special controls document. The guidance does not include patient labeling. The need for a Special Controls document was discussed at the FDA panel meeting in 2011.
[73] Guidance on Medical Device Patient Labeling, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070782.htm.

provide the manufacturer flexibility in describing adverse effects.

Industry standards and best practices come into play in the provision for and content of patient brochures or patient information. Such brochures or information are provided for TVT devices, for example by Ethicon, Caldera, and AMS.[74]

III. Ethicon TVT Devices

A. Ethicon Gynecare TVT Product Name Variations

Each of Ethicon's TVT devices is known by other project or product names.[75] In this report, the same device may be identified by one of the alternative names. For example:

Name	Some Alternative Names
TVT	TVT Classic TVT PROLENE Mesh TVT Standard Gynecare TVT TVT Retropubic TVT-R
TVT-AA	Abdominal Approach TVT Abdominal TVT Blue
TVT-O	TVT Obturator Mulberry
TVT Abbrevo	TVT Twins
TVT Exact	TVT Retropubic Refresh
TVT Secur	TVT-S TVT Universal Mini sling
TVT-D	TVTD

B. Relevant ETHICON Regulatory Submissions

I examined 510(k) records to help construct the table of the history of ETHICON TVT and mesh submissions in this section of my report. I searched the FDA 510(k) database as referenced in the table to identify additional submissions not included in the records provided by counsel. I ordered the submissions by 510(k) number in the table.

The TVT devices intended to treat SUI are all grouped under the surgical mesh classification as Class II, 21 CFR §878.3300.

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[74] See report for Ethicon, Caldera https://www.calderamedical.com/DesaraFamilyPatientBrochure_RevC_01_15_14_FINAL_single%20pages.pdf, AMS https://americanmedicalsystems.com/en/patients/women/female-incontinence.html.

[75] DEPO.ETH.MESH.00000067.

Since PROLENE polypropylene is a key constituent of the ETHICON TVT devices, I also examined the first FDA regulatory approval submission for a product containing PROLENE. FDA approved a New Drug Application (NDA), NDA 16-374, for the predicate PROLENE polypropylene suture on April 16, 1969.[76] The labeling for the suture approved in 1969 included the adverse reaction "Minimum transitory reactions have been reported."[77] The suture NDA is referenced in the 510(k) for the TVT Classic.

The NDA later transitioned to the Center for Devices and Radiological Health as a premarket approval application (PMA). In all there were 35 supplemental application approvals for this NDA/PMA. One supplement, S34, approved on October 13, 1988, provided for additional language in the package insert stating:[78]

> PROLENE Polypropylene Suture, U.S.P. causes a minimal, transient acute inflammatory reaction. This is followed by the formation of a microscopic layer of fibrous tissue around the suture. The suture is not absorbed nor is it subject to degradation or weakening by the action of tissue enzymes.

FDA reclassified eight types of sutures, including PROLENE sutures, from Class III to Class II devices and promulgated the reclassification to Class II under 21 CFR §878.5010, Nonabsorbable polypropylene surgical suture. This type of device must meet a special control guidance document.[79]

As noted, FDA classified surgical mesh as Class II under 21 CFR §878.3300. In classifying the mesh the Classification Panel and FDA evaluated the type of device's safety and effectiveness according to 21 CFR §860.84.

Catherine Beath, an Ethicon executive, testified, “there was a pre-amendment PROLENE mesh.”[80] The 510(k) for the PROLENE mesh cleared under K962530 refers to the pre-amendments mesh and also states that the mesh "is constructed of filaments of extruded polypropylene identical in composition to that used in PROLENE polypropylene suture..."[81] The 510(k) for the TVT Classic states "The TVT device...is composed of polypropylene mesh...This is the same Polypropylene Mesh that is used to fabricate PROLENE polypropylene mesh (K962530). The PROLENE mesh is fabricated from polypropylene strands. These same strands are used to fabricate PROLENE polypropylene Nonabsorbable Surgical Suture (NDA/PMA #16-374)..."[82] The TVT-O contains a blue polypropylene cleared under K012628 and K001122 which in turn are again predicated upon K962530.[83]

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[76] HMESH_ETH_00019754.
[77] HMESH_ETH_00024172.
[78] HMESH_ETH_00028327-00028341.
[79] Reclassification effective July 5, 1990: HMESH_ETH_00028685-00028686, FR Vol.68, Number 106 (Tuesday, June 3, 2003). See 21 CFR §878.5010 for special control.
[80] Catherine Beath deposition, 3/26/2012, Page 55:16.
[81] ETH_02254.
[82] ETH.MESH.00371506.
[83] ETH-01654.

FDA recently cleared a 510(k) for PROLENE Polypropylene Sutures, K133356.[84] The summary notes that the 510(k) was for labeling changes to the suture.

TABLE OF ETHICON TVT and MESH DEVICES CLEARED BY FDA

K Number	Device Name	Material/Change	Predicate(s)	Submitted Data
K962530[85] 8/9/96	PROLENE Polypropylene Mesh Nonabsorbable Synthetic Surgical Mesh	Knitted polypropylene identical to PROLENE sutures Additional sizes and key hole shape	pre-amendment PROLENE polypropylene mesh	Bench, preclinical
K972412 9/10/97	ETHICON PROLENE Polypropylene Mesh Hernia Device Nonabsorbable Synthetic Surgical Mesh Implant[86]	PROLENE polypropylene	BARD Marlex mesh PerFix Plug	preclinical
K974098[87] 1/28/98 Traditional 510(k)	Tension Free Vaginal Tape (TVT) System	Polypropylene mesh identical to PROLENE polypropylene suture and mesh	Protegen Sling[88] PROLENE Suture NDA/PMA 16-374 PROLENE mesh	Bench, preclinical and clinical data
K984220 2/23/1999	PROLENE (Polypropylene) Hernia System[89]	Pre-shaped	PROLENE Hernia System	No data indicated in record
K001122 5/23/2000	PROLENE Soft[90] (polypropylene) nonabsorbable Synthetic Surgical Mesh	Diameter of monofilament and pigmented strands	K962530 and Mersilene mesh (polyester fiber mesh) preamendments	Bench, K962530 preclinical, clinical based on prior PROLENE mesh
K002672 11/22/2000	VYPRO Mesh[91]	Mix of polypropylene and polyglactin	PROLENE Mesh and VICRYL (polyglactin 910) Mesh	Bench
K010722 4/27/01	Polypropylene 3D Patch[92]	Three-dimensional	PROLENE Hernia system and Bard Marlex PerFix Plug	Nonclinical laboratory
K012628 10/26/01 Traditional	GYNECARE[93] Tension-Free Vaginal Tape (TVT) Blue System, TVT-AA	Addition of blue pigmented polypropylene fibers interwoven with	K974098 K001122 K962530	Bench, preclinical, K974098 clinical data

[84] Recent 510(k) for PROLENE Suture.http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K133356.
[85] ETH-02240-02273.
[86] accessdata.fda.gov/cdrh_docs/pdf/K972412.pdf.
[87] 1998 submission, see Attachment.
[88] Removed from market; no effect on other products based on lack of evidence of FDA action.
[89] accessdata.fda.gov/cdrh_docs/pdf/K984220.pdf.
[90] ETH-01646-01818.
[91] accessdata.fda.gov/cdrh_docs/pdf/K002672.pdf.
[92] accessdata.fda.gov/cdrh_docs/pdf/K010722.pdf.
[93] 2001 submission, see Attachment.

510(k)		unpigmented fibers, abdominal guides		
K013718 1/8/2002	GYNEMESH[94] PROLENE Soft Nonabsorbable Synthetic Surgical Mesh for Pelvic Floor Repair	Same as K001122 Pelvic floor claim	K001122 K962530 MERSILENE	K00122 for bench testing, K962530 for preclinical, published literature for clinical
K031925 9/17/03	PROCEED[95] Trilaminate Surgical Mesh	Layers of PS, regular poly, ORC and polydioxanone	PROLENE soft Polypropylene Mesh	Nonclinical and in-vivo testing
K033337	ULTRAPRO Mesh[96]	No FDA info	No FDA info	Animal testing
K033568 12/8/03 Special 510(k)	GYNECARE TVT Obturator Device[97] Consists of tape with passers and winged guide	Replacement of needles with plastic tube receptacles to accommodate Helical Passer, trans-obturator "inside out" approach	K974098 TVT Classic K012628 TVT Blue with guides K02356 (sic) AMS helical needles	Predicate comparison; conformity to design controls and statement of verification testing
K042603 12/22/04	GYNECARE PROLENE Fastener System	PROLENE	Mitek meniscal fastener	In-vitro and in-vivo studies
K052401 11/28/05 Traditional 510(k)	GYNECARE TVT SECUR System[98]	Material change and needles fixed to implant; change in implantation method	K033568 K012628 K974098	Bench, Preclinical and cadaver data
K060713 5/25/06	PROCEED[99] Surgical Mesh	Manufacturing change	PROCEED Trilaminate Mesh	manufacturing data
K061533 12/11/06	PROCEED Ventral Patch[100]	Not clear.	PROLENE Soft PROCEED BARD Ventralex VICRYL ETHIBOND	Preclinical, bench and animal
K063562 2/26/07	GYNECARE PROSIMA Pelvic Floor Repair Systems	Precut GYNECARE GYNEMESH PS Mesh Implants and instruments; device balloon assembly; silicon	GYNECARE GYBEMESH PS Nonabsorbable PROLENE Soft Mesh Silimed Vaginal Stent	bench
K070224 4/17/07	ULTRAPRO Plug[101]	Plug and patch	ULTRAPRO mesh BARD Mesh PerFix Plug	Bench and animal
K071249 6/5/07	ULTRAPRO Hernia System[102]	Change in materials	PROLENE hernia system ULTRAPRO mesh	Bench and animal
K071512 5/15/08	GYNECARE PROLIFT Total, Anterior, and Posterior Pelvic Floor Repair Systems	PROLIFT: Same as GYNEMESH PS; precut mesh and instruments	PROLIFT: K013718 AMS Apogee K040537 AMS Perigee K040623 PROLIFT+M:	Bench, Cadaver, clinical

[94] ETH00797-00927.
[95] accessdata.fda.gov/cdrh_docs/pdf3/K031925/pdf.
[96] www.fda.gov/ohrms/dockets/ac/08/briefing.
[97] 2003 submission, see Attachment.
[98] 2005 submission, see Attachment.
[99] accessdata.fda.gov/cdrh_docs/pdf6/K060713.pdf.
[100] accessdata.fda.gov/cdrh_docs/pdf6/K061533.pdf.
[101] accessdata.fda.gov/cdrh_docs/pdf7/K070224.pdf.
[102] accessdata.fda.gov/cdrh_docs/pdf7/K071249.pdf.

	GYNECARE PROLIFT+M Total, Anterior, and Posterior Pelvic Floor Repair Systems[103]	PROLIFT+M: Same as Ultrapro Mesh; precut mesh and instruments	K033337 Ultrapro Mesh K013718 K040537 K040623	
K082216 9/5/08	ETHICON Mesh[104]	Absorbable and nonabsorbable polymers	GYNECARE GYNEMESH PS PROLIFT+M	Functional testing
K093932 4/9/10	ETHICON Physiomesh[105]	Mesh layers, low profile	PROCEED mesh ULTRAPRO Hernia System ULTRAPRO Mesh	Bench and animal
K100485 3/16/10 Special 510(k)	GYNECARE TVT Exact Continence System[106]	accessory changes	GYNECARE TVT	Trocar tests
K100936 7/1/10 Traditional 510(k)	GYNECARE TVT ABBREVO[107]	Change in assembly and accessories	GYNECARE TVT	Bench and cadavers
K113205 6/12/12	ARTISYN Y SHAPED mesh[108]	Y shaped mesh	ALYTE mesh GYNEMESH M RESTORELLE Y	Mechanical testing
K132054 8/23/13 Special 510(k)	TVT Exact Continence System[109]	Introducer/tip change	TVT EXACT K100485	bench testing
K141516 10/23/14 Traditional 510(k)[110]	Ethicon Physiomesh	Macroporous mesh composed of knitted polypropylene, and polydioxanone fibers laminated to absorbable poliglecaprone	K093932 Physiomesh BARD Ventrio Patch Parietex Mesh	Bench testing per guidance, biocompatibiloty tests, animal implant test

C. Description of TVT-O

The Ethicon TVT-O device, the subject of this litgiation, is described as follows:[111]

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[103] ETH-02015-02238, 01324-01637, 00950-01310, 01903-02014, 01318-01323.
[104] accessdata.fda.gov/cdrh_docs/pdf8/K082216.pdf.
[105] accessdata.fda.gov/cdrh_docs/pdf9/K093932.pdf.
[106] accessdata.fda.gpv/cdrh_docs/pdf10/K100485.pdf.
[107] accessdata.fda.gov/cdrh_docs/pdf10/K100936.pdf.
[108] accessdata.fda.gov/cdrh_docs/pdf/K113205.pdf.
[109] Exact, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K132054.
[110] Physiomesh, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K141560.

DESCRIPTION

The GYNECARE TVT Obturator System is a sterile, single patient use procedure kit consisting of:

GYNECARE TVT Obturator device

The GYNECARE TVT Obturator device is a sterile, single patient use device, consisting of one piece of undyed or blue (Phtalocyanine blue, Color index Number 74160) PROLENE™ polypropylene mesh (tape) approximately 1/2 x 18 inches (1.1 x 45 cm) covered by a plastic sheath overlapping in the middle. Plastic tube receptacles are attached at each end. PROLENE polypropylene mesh is constructed of knitted filaments of extruded polypropylene strands identical in composition to that used in PROLENE polypropylene non-absorbable surgical suture. This material, when used as a suture, has been reported to be non-reactive and to retain its strength indefinitely in clinical use. PROLENE mesh is knitted by a process that interlinks each fiber junction and that provides elasticity in both directions. This bi-directional elastic property allows adaptation to various stresses encountered in the body.

GYNECARE TVT Helical Passers

The GYNECARE TVT Helical Passers are two stainless steel, curved wire passers with plastic handles that are designed to deliver the GYNECARE TVT Obturator device. Helical Passers are provided as left and right units, pre-assembled to the GYNECARE TVT Obturator device. The Helical Passer MUST not be bent or deformed in any way.

GYNECARE TVT Atraumatic Winged Guide

The GYNECARE TVT Atraumatic Winged Guide is a stainless steel accessory instrument, which facilitates the passage of the GYNECARE TVT Helical Passers through the dissection tract.

IV. Surgical Mesh Products for Treatment of Stress Urinary Incontinence (SUI), FDA Public Health Notice in 2008, FDA 2011 Panel Meeting, FDA Updated PHN in 2013, and Surgical Mesh for POP Reclassification in 2016

A. SUI and Treatment Options

The following is a partial excerpt on FDA's web site describing SUI and treatment options:[112]

> Stress urinary incontinence (SUI) is a leakage of urine during moments of physical activity that increases abdominal pressure, such as coughing, sneezing, laughing, or exercise. SUI is the most common type of urinary incontinence in women.
>
> SUI can happen when pelvic tissues and muscles, which support the bladder and urethra, become weak and allow the bladder "neck"

[111] ETH.MESH.02340903.

[112] Stress Urinary Incontinence, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm284109.htm. Viewed on January 29, 2016.

> (where the bladder and urethra intersect) to descend during bursts of physical activity. This descent can prevent the urethra from working properly to control the flow of urine. SUI can also occur when the sphincter muscle that controls the urethra weakens. The weakened sphincter muscle is not able to stop the flow of urine under normal circumstances and when there is an increase in abdominal pressure. Weakness may occur from pregnancy, childbirth, aging, or prior pelvic surgery. Other risk factors for SUI include chronic coughing or straining, obesity and smoking.
>
> It is important for you to consult with your health care provider for proper diagnosis of SUI…
>
> Women have both non-surgical and surgical treatment options to treat SUI…
>
> Surgery to decrease or prevent urine leakage can be done through the vagina or abdomen. The urethra or bladder neck is supported with either stitches alone or with tissue surgically removed from other parts of the body such as the abdominal wall or leg (fascial sling), with tissue from another person (donor tissue) or with material such as surgical mesh (mesh sling). Surgical mesh in the form of a "sling" (sometimes called "tape") is permanently implanted to support the urethra or bladder neck in order to correct SUI. This is commonly referred to as a "sling procedure."
>
> The use of surgical mesh slings to treat SUI provides a less invasive approach than non-mesh repairs, which require a larger incision in the abdominal wall. The multi-incision sling procedure can be performed using three incisions, in two ways: with one vaginal incision and two lower abdominal incisions, called retropubic; or with one vaginal incision and two groin/thigh incisions, called transobturator. There is also a "mini-sling" procedure that utilizes a shorter piece of surgical mesh, which may be done with only one incision.

B. FDA's Summary of the Development of Surgical Mesh for the Treatment of SUI

The FDA Executive Summary from a September 2011 FDA panel meeting on SUI and POP devices provides a brief overview of the development of surgical mesh for the treatment of SUI and pelvic organ prolapse.[113]

> "Surgical mesh was a pre-amendments device and was classified into Class II (21 CFR 878.3300). Since the 1950s, surgical mesh has been used to repair abdominal hernias. In the 1970s, gynecologists began using surgical mesh products indicated for hernia repair for abdominal repair of POP, and in the 1990s, gynecologists began using surgical mesh for surgical treatment of

[113] FDA Executive Summary, September 8, 2011, OB/Gyn Advisory Committee Meeting, page 5, http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/ucm262488.htm.

SUI and vaginal repair of POP. To do so, surgeons would cut the mesh to the desired shape for SUI repair or POP repair and then place the mesh through a corresponding incision. Over time, manufacturers responded to this clinical practice by developing mesh products specifically designed for SUI and POP repair.

In 1996, the Surgical Fabrics (ProteGen Sling) device manufactured by Boston Scientific Corporation became the first pre-configured surgical mesh product cleared via the 510(k) pathway for surgical treatment of SUI. (The ProteGen Sling was cleared with an indication for "pubourethral support," a phrase which implies an indication for treatment of SUI.) However, use of mesh in SUI repair, referred to as slings or tape, did not become common until after the introduction of the Tension-Free Vaginal Tape (TVT™) System, manufactured by Ethicon/GYNECARE, in 1998. This system was based on the work by Ulmsten and colleagues with the Ethicon PROLENE hernia mesh. In 2002, GYNEMESH® PS, also manufactured by Ethicon/GYNECARE, became the first pre-configured surgical mesh product cleared for POP repair.

Over the next few years, surgical mesh products evolved into "kits" that included tools to aid in the delivery/insertion of the mesh. The first kit for SUI repair, the Island Biosurgical Bladder Neck Suspension Kit manufactured by Island Biosurgical, Inc., was cleared in 1997. The first kits for POP repair, the AMS Apogee™ System and the AMS Perigee™ System, both manufactured by American Medical Systems, Inc., were cleared in 2004. Surgical mesh kits continue to evolve in regards to introducer instrumentation, tissue fixation anchors, surgical technique, and incorporation of absorbable materials into the mesh intended to increase material compliance.

The FDA premarket notification review process did not request original clinical studies to support clearance of surgical mesh indicated for treatment of SUI or POP. Attempts to establish clinical effectiveness were undertaken later by the clinical community with clinical trials, published studies, and systematic reviews/meta-analyses. Some of this published literature was incorporated into later 510(k) submissions to support market clearance.

Premarket clearance of surgical mesh indicated for POP and SUI repair was typically based on pre-clinical bench and animal studies as described in the FDA Guidance Document "Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh" issued on March 2, 1999 (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073791.pdf)."

"From 1992-2010, the FDA cleared 168 510(k)s for surgical mesh with urogynecologic indications."

C. FDA Public Health Notification of October 20, 2008, Concerning Mesh for Pelvic Organ Prolapse and SUI

FDA issued a 2008 Public Health Notification (PHN) on Surgical Mesh, following its examination of adverse events related to various surgical meshes sold by numerous different manufacturers.[114]

The PHN states:

> This is to alert you to complications associated with transvaginal placement of surgical mesh to treat Pelvic Organ Prolapse (POP) and Stress Urinary Incontinence (SUI). Although rare (emphasis added), these complications can have serious consequences. Following is information regarding the adverse events that have been reported to the FDA and recommendations to reduce the risks.
>
> **Nature of the Problem**
>
> Over the past three years, FDA has received over 1,000 reports from nine surgical mesh manufacturers of complications that were associated with surgical mesh devices used to repair POP and SUI. These mesh devices are usually placed transvaginally, utilizing tools for minimally invasive placement.
>
> The most frequent complications included erosion through vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and/or incontinence. There were also reports of bowel, bladder, and blood vessel perforation during insertion. In some cases, vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia.
>
> Treatment of the various types of complications included additional surgical procedures (some of them to remove the mesh), IV therapy, blood transfusions, and drainage of hematomas or abscesses.
>
> Specific characteristics of patients at increased risk for complications have not been determined. Contributing factors may include the overall health of the patient, the mesh material, the size and shape of the mesh, the surgical technique used, concomitant procedures undertaken (e.g. hysterectomy), and possibly estrogen status.
>
> **Recommendations**
>
> Physicians should:
> - Obtain specialized training for each mesh placement technique, and be aware of its risks.

[114] Public Health Notice, originally http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm061976.htm but removed by FDA. Referenced in http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm262301.htm. Viewed on 3/17/14.

- Be vigilant for potential adverse events from the mesh, especially erosion and infection.
- Watch for complications associated with the tools used in transvaginal placement, especially bowel, bladder and blood vessel perforations.
- Inform patients that implantation of surgical mesh is permanent, and that some complications associated with the implanted mesh may require additional surgery that may or may not correct the complication.
- Inform patients about the potential for serious complications and their effect on quality of life, including pain during sexual intercourse, scarring, and narrowing of the vaginal wall (in POP repair).
- Provide patients with a written copy of the patient labeling from the surgical mesh manufacturer, if available.

FDA often provides industry a draft of its public health notice and solicits comments before FDA finalizes the document. Although FDA may consider comments from industry, Catherine Beath from Ethicon correctly noted in her testimony "FDA ultimately owns the final version."[115]

D. September 2011 FDA Advisory Panel Review of Clinical Data Supporting the Safety and Effectiveness of Vaginal Slings

The data supporting the safety and effectiveness of TVT-O was discussed at the September 9, 2011 meeting of the FDA Obstetrics and Gynecological Panel of the Medical Devices Advisory Committee. While all the data presented do not relate solely to ETHICON devices it is important to understand the overall discussions regarding this type of product.

The Transvaginal Mesh Industry Working Group provided a report, dated August 30, 2011, to the Panel and a presentation summarizing the report was given at the panel meeting. ETHICON participated in the creation of the report and presentation to the panel.

The report describes the advances in surgical mesh devices for SUI beginning with use of autologous tissue, xenografts and allografts and associated concerns for their long-term effectiveness, followed by development of synthetic mesh, retropubic and transobturator approaches and single incision slings. The paper notes "patient selection and surgical technique are critical for the success of any surgical procedure…Physicians must be knowledgeable in pelvic floor anatomy and surgery."

The Working Group reviewed MDR reports. As noted, "This review of the overall MDR rate, as well as rates associated with serious adverse events (SAE), indicated that while there was an increase in adverse events overall, the rate remains low with an average rate of 0.13% for the 2008 to 2010 period. When comparing the number of serious adverse events to the total adverse events for each time period, it was determined that the 2005 to 2007 period had a 33% rate of SAE/Total AE (0.02%SAE) and 2008 to 2010 had a rate of 31% (0.04% SAE). Therefore, the ratio between serious adverse events and total adverse events has remained constant between the two time periods. While the Working Group

[115] Catherine Beath deposition, 3/26/2012, Page 261:24-25.

analysis is still saddled with many of the limitations of the MAUDE database itself, the usefulness of the denominator information allows a better analysis of the change in event rates."

The Working Group assessed the clinical literature, adverse effects and effectiveness, summarized in appendices to the report, noting "There is strong evidence available to date that demonstrates that the midurethral sling has a favorable benefit/risk profile and that these procedures are valuable treatment options for women suffering from SUI. The risk and benefit is well characterized and understood by the clinical community."

The FDA Executive Summary provided to the Advisory Panel for the meeting states:[116]

> "The FDA did not request original clinical performance data for either the first generation minimally invasive suburethral slings or the single-incision mini-slings. A substantial number of quality clinical trials, as well as systematic reviews, have been published for the first generation minimally invasive slings that provide evidence of safety and effectiveness of these devices."

Based on its assessment of the available safety and effectiveness data FDA reported the following conclusions regarding "full-length" vaginal slings:

> "After considering all available data on both safety and effectiveness, and considering the risk/benefit profile, it appears that new premarket clinical trials are not warranted for minimally invasive slings for SUI unless the device has new features (e.g. new polymer or coating) that could affect device performance. The FDA recognizes, however, that the strength of this conclusion is limited by what is largely short duration (2 years) follow-up in the literature with limited data available past 3 years of follow-up.
>
> The regulatory threshold for the FDA to request clinical outcomes data is different for the premarket setting compared to the postmarket setting. The FDA believes that whereas the published literature provides sufficient clinical performance data to support new premarket notifications for the first generation SUI sling, it may be appropriate to require special postmarket surveillance studies to improve the FDA's understanding of the safety profile of all types of minimally invasive slings (including mini-slings).
>
> Finally, the FDA recognizes that all minimally invasive synthetic slings (including mini-slings) are associated with risk of failure as well as patient injury. The FDA believes, however, that the peer reviewed literature affords sufficient understanding of the nature and severity of risks from minimally invasive synthetic slings to enable FDA to review these devices under the Special Controls provisions of 510(k) premarket

[116] FDA Executive Summary, September 9, 2011, OB/Gyn Advisory Committee Meeting, http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM270402.pdf.

> notification as Class II medical devices. The FDA is not proposing to reclassify these devices from Class II to Class III (Premarket Approval)."

The Panel concluded in response to a question from FDA on retropubic and transobturator suburethral slings:[117]

> "The panel consensus was that the safety and effectiveness of these devices is well-established. Unless there are significant material changes or changes in the surgical access (including introducer instrumentation), premarket clinical studies would generally not be necessary. The panel consensus was that consideration should be made to better characterize low frequency life-altering adverse events, potentially via collaboration with industry and use of existing large-scale health databases. The panel did not believe that 522 postmarket studies would be an appropriate mechanism for this, and the consensus was that 522 postmarket studies for these devices are not necessary."

E. March 27, 2013, FDA Updated Considerations About Surgical Mesh for SUI

FDA posted the following updated considerations concerning SUI (emphasis added):[118]

> Mesh sling procedures are currently the most common type of surgery performed to correct SUI. Based on industry estimates, there were approximately 250,000 of these procedures performed in 2010.
>
> While all surgeries for SUI carry some risks, it is important for you to understand the unique risks and benefits for surgical mesh slings used in SUI repair.
>
> In order to better understand the use of surgical mesh slings for SUI and evaluate their safety and effectiveness, the FDA held a panel meeting of scientific experts (Obstetrics and Gynecology Devices Panel of the Medical Device Advisory Committee) in September 2011 and conducted a systematic review of the published scientific literature from 1996 to 2011. For surgical mesh slings used for SUI, both the panel and the FDA's review found that:
>
> - The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year. Longer follow-up data is available in the literature, but there are fewer of these long-term studies compared to studies with one-year follow-up…
> - Mesh sling surgeries for SUI have been reported to be successful in approximately 70 to 80 percent of women at

[117] FDA 24 hour memo, http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM271769.pdf.

[118] Considerations about Surgical Mesh for SUI, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm345219.htm.

one year, based on women's reports and physical exams. Similar effectiveness outcomes are reported following non-mesh SUI surgeries.

- The use of mesh slings in transvaginal SUI repair introduces a risk not present in traditional non-mesh surgery for SUI repair, which is mesh erosion, also known as extrusion.
- Erosion of mesh slings through the vagina is the most commonly reported mesh-specific complication from SUI surgeries with mesh. The average reported rate of mesh erosion at one year following SUI surgery with mesh is approximately 2 percent. Mesh erosion is sometimes treated successfully with vaginal cream or an office procedure where the exposed piece of mesh is cut. In some cases of mesh erosion, it may be necessary to return to the operating room to remove part or all of the mesh.
- The long-term complications of surgical mesh sling repair for SUI that are reported in the literature are consistent with the adverse events reported to the FDA.
- The complications associated with the use of surgical mesh slings currently on the market for SUI repair are not linked to a single brand of mesh.

The FDA conducted a review of Medical Device Reports (MDRs) received from Jan. 1, 2008 through Sept. 30, 2011. During this time frame the FDA received 1,876 reports of complications associated with surgical mesh devices used to repair SUI. The most common complications reported through MDRs for surgical mesh slings for SUI repair, in descending order of frequency, include: pain, mesh erosion through the vagina (also called exposure, extrusion or protrusion), infection, urinary problems, recurrent incontinence, pain during sexual intercourse (dyspareunia), bleeding, organ perforation, neuro-muscular problems and vaginal scarring. Many of these complications require additional medical intervention, and sometimes require surgical treatment and/or hospitalization. With the exception of mesh erosion, the above complications can occur following a non-mesh surgical repair for SUI…While MDRs are a valuable source of information, this passive surveillance system has notable limitations, including the potential submission of incomplete or inaccurate data, under-reporting of events, lack of denominator data (number of implants), and the lack of report timeliness.

Information for Health Care Providers for SUI

The 2013 update to the FDA web site on SUI includes the following information for health care providers for SUI (emphasis added):[119]

- Obtain specialized training for each SUI mesh placement technique.
- Be vigilant for potential adverse events from the mesh sling, such as erosion.

[119] Recommendations for Health Care Providers, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm345221.htm.

- Watch for complications associated with the use of the tools used in transvaginal placement of the mesh sling during the surgical procedure, such as bladder perforations.
- Inform the patient about her choice to have incontinence repair with or without a mesh sling. The patient should understand:
    - the likely success of transvaginal SUI surgery with mesh compared to non-surgical treatment options and non-mesh surgery based on the individual patient factors.
    - the potential postoperative complications of a mesh sling surgery compared to non-mesh surgery and their effect on quality of life.
    - that there is limited information about outcomes after one year.
    - whether or not mesh will be used in the repair, and if so, which specific product will be used.
    - that a mesh sling is a permanent implant.
    - that, as with any SUI surgery, the use of surgical mesh for SUI can make any future surgical repairs more challenging and can put the patient at risk for additional complications and surgeries.
- Ensure that the patient understands the postoperative risks and potential complications of mesh sling surgery.
- Provide patients with a copy of the patient labeling or brochure, if available from the manufacturer

Information for Patients for SUI

The 2013 updated FDA web site contains the following excerpts directed to the patient:[120]

> Ask your surgeon about all SUI treatment options, including non-surgical options and surgical options that do and do not use mesh slings. It is important for you to understand why your surgeon may be recommending a particular treatment option to treat your SUI.
>
> Any surgery for SUI may put you at risk for complications, including additional surgery.

F. Section 522 Orders

Postmarket surveillance under section 522 of the Federal Food, Drug, and Cosmetic Act (the act) is one means by which the Food and Drug Administration (FDA) can obtain additional safety and/or effectiveness data for a device after it has been cleared through the premarket notification (510(k)) process.

On January 3, 2012 FDA issued 522 postmarket study orders to various mesh manufacturers, including five orders to ETHICON for specific surgical mesh products: GYNEMESH PS, PROLIFT, PROLIFT +M, Prosima and

[120] Recommendations for Patients, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm345230.htm.

TVT Secur.[121] The orders requested postmarket surveillance studies and specified the questions to be answered by the studies and elements of the study protocols.[122] Notably, FDA did not issue any such orders with respect to TVT-O.

G. FDA Reclassifies Only Surgical Mesh for Pelvic Organ Prolapse Repair in 2016

On May 21, 2014, FDA published a proposal to reclassify surgical mesh for transvaginal pelvic organ prolapse (POP) repair from Class II to Class III.[123] FDA also proposed to reclassify "specialized" urogynecological surgical mesh instrumentation from Class I to Class II. The FDA proposed order states the mesh reclassification does not include surgical mesh indicated for surgical treatment of stress urinary incontinence, sacrocolpopexy (transabdominal POP repair), hernia repair, and other non-urogynecologic indications. The proposal includes entirely new classification regulations for mesh used in POP repair and for the specialized urogynecological instruments. On January 5, 2016, FDA published a final order reclassifying surgical mesh for POP.[124]

V. FDA Takes No Regulatory Action on TVT-O; Professional Associations and UK National Institute Support the Safety and Effectiveness of Full-Length/Suburethral/TVT Vaginal Slings Like TVT-O

In Section IV above I describe several FDA activities related to transvaginal slings. These are activities related to the transvaginal sling class of products and not to any one type of sling. FDA has taken no adverse action specifically on TVT-O and professional organizations support the use of transvaginal slings.

A. FDA issued no postmarket study requirements, no special controls, and or labeling recommendations for TVT Classic and TVT-O

In this report I outline the FDA enforcement actions it may take if it finds a device to be in violation of the laws and regulations it administers. There are other actions FDA may take to help ensure the safety and effectiveness of devices. FDA has taken no action to control or limit the legal distribution of TVT-O.

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[121] 522 study listing, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm?start_search=E#E.
[122] ETH.MESH.030467737-030467740.
[123] FDA proposed reclassification of POP mesh, and instruments for POP and SUI, https://www.federalregister.gov/articles/2014/05/01/2014-09907/reclassification-of-surgical-mesh-for-transvaginal-pelvic-organ-prolapse-repair-and-surgical.
[124] 81 FR 353.

FDA has never issued any postmarket Section 522 postmarket study order for Gynecare TVT-O or for its predicate TVT Classic. These devices have remained on the market for the last 12 and 16 years respectively.

FDA has not promulgated any Class II special controls for TVT devices.

FDA has not modified the surgical mesh guidance since the 2011 panel meeting.

FDA has not recommended any labeling changes for TVT devices.

FDA has taken no enforcement action against TVT-O.

B. 2011 American Urologic Association (AUA) Statement

In November 2011 the AUA published a position statement regarding the use of vaginal mesh for the surgical treatment of stress urinary incontinence. It states:[125]

> Suburethral synthetic polypropylene mesh sling placement is the most common surgery currently performed for SUI. Extensive data exist to support the use of synthetic polypropylene mesh suburethral slings for the treatment of female SUI, with minimal morbidity compared with alternative surgeries. Advantages include shorter operative time/anesthetic need, reduced surgical pain, reduced hospitalization, and reduced voiding dysfunction. Mesh-related complications can occur following polypropylene sling placement, but the rate of these complications is acceptably low. Furthermore, it is important to recognize that many sling-related complications are not unique to mesh surgeries and are known to occur with non-mesh sling procedures as well. It is the AUA's opinion that any restriction of the use of synthetic polypropylene mesh suburethral slings would be a disservice to women who choose surgical correction of SUI.
>
> Multiple case series and randomized controlled trials attest to the efficacy of synthetic polypropylene mesh slings at 5-10 years. This efficacy is equivalent or superior to other surgical techniques. There is no significant increase in adverse events observed over this period of follow-up. Based on these data, the AUA Guideline for the Surgical Management of Stress Urinary Incontinence (2009) concluded that synthetic slings are an appropriate treatment choice for women with stress incontinence, with similar efficacy but less morbidity than conventional non-mesh sling techniques. The AUA Guideline also indicates that intra-operative cystoscopy should be performed during all synthetic sling procedures to identify urinary tract injury.
>
> The AUA strongly agrees with the FDA that a thorough informed consent should be conducted prior to synthetic sling surgery. The AUA also agrees that surgeons who wish to perform synthetic sling surgery should:
> • Undergo rigorous training in the principles of pelvic anatomy and pelvic surgery.
> • Be properly trained in specific sling techniques.

[125] nihttp://www.auanet.org.

- Be able to recognize and manage complications associated with synthetic mesh sling placement.

C. 2013 American Urogynecologic Society (AUGS) Statement

On March 26, 2013, the AUGS published a statement entitled "Position Statement on Restriction of Surgical Options for Pelvic Floor Disorders."[126] It reads "The American Urogynecologic Society strongly opposes any restrictions by state or local medical organizations, healthcare systems, or insurance companies which ban currently available surgical options performed by qualified and credentialed surgeons on appropriately informed patients with pelvic floor disorders….Our Justification for this position statement is described below. (parts of justification noted below)

1. A complete restriction on the use of surgical mesh was not the stated intent of the FDA safety communication.

2. The decision on surgical alternatives should be made by the patient and her surgeon.

3. A ban on surgical mesh would prohibit the surgical studies mandated by the FDA and recommended by the NIH, ACOG, and AUGS.

4. In some circumstances transvaginal mesh for pelvic organ prolapse may be the most appropriate surgical option.

5. Any restriction of mesh slings for the treatment of stress urinary incontinence is clearly not supported by any professional organization or the FDA.

However, it is particularly important to note that full-length midurethral slings were excluded from the (FDA) mandated post marketing studies. In a recent study involving 53 expert urologists and urogynecologists (of whom >90% were fellowship trained) and who could select among many surgical options, the full-length synthetic midurethral sling was the preferred opinion in 93% for the surgical treatment of primary stress incontinence. Full length midurethral slings, both retropubic and transobturator, have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard of care for stress urinary incontinence surgery.

6. Any restriction of mesh placed abdominally for the treatment of prolapse is clearly not supported by any professional organization or the FDA.

7. Instead of a ban on mesh we recommend the implementation of credentialing guidelines so that mesh procedures are performed by qualified surgeons.

[126] http://www.augs.org/p/bl/et/blogid=6&blogaid=160.

D. National Institute for Health and Care Excellent (NICE); Urinary Incontinence: The management of urinary incontinence in women[127]

The National Institute for Health and Care Excellence (NICE) provides national guidance and advice in the UK to improve health and social care. The September 2013 NICE guidance on treatment of urinary incontinence states the following regarding synthetic tapes:

> When offering a synthetic mid-urethral tape procedure, surgeons should: use procedures and devices for which there is current high quality evidence of efficacy and safety…use a device manufactured from type 1 macroporous polypropylene tape…The guideline only recommends the use of tapes with proven efficacy based on robust RCT evidence (emphasis added). However, technological advances are frequent, therefore the choice of tape should include devices that are shown in future clinical trials to have equal or improved efficacy at equal or lower cost. At the time of publication (September 2013) the following met the Guideline Development Group criteria… TVT or Advantage for a "bottom-up retropubic approach.

The guideline does not recommend culposuspension or types of biological slings for the treatment of stress UI. It also provides long-term outcome data to aid the physician in informing their patients.

E. 2014 AUGS-Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) Statement

On January 3, 2014, AUGS-SUFU published a joint notice entitled "Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence."[128] The statement reads, in part, as follows:

> ***The polypropylene mesh midurethral sling is the recognized worldwide standard of care for the surgical treatment of stress urinary incontinence. The procedure is safe, effective, and has improved the quality of life for millions of women.***
>
> **Introduction**
>
> The purpose of this position statement by the American Urogynecologic Society (AUGS) and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) is to support the use of the midurethral sling in the surgical management of stress urinary incontinence, the type of urine leakage generally associated with coughing, laughing and sneezing.
>
> Developed in the early 1990's, midurethral slings (MUS) treat stress urinary incontinence (SUI) in a minimally invasive, generally outpatient procedure. This technique utilizes a small mesh strip composed of monofilament polypropylene placed through the vagina under the mid-urethra exiting from 2 small sites in either the suprapubic or groin areas.

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[127] NICE guideline: http://guidance.nice.org.uk/CG171/NICEGuidance/pdf/English.

[128] http://sufuorg.com/docs/news/AUGS-SUFU-MUS-Position-Statement-APPROVED-1-3-2014.aspx.

SUI is a highly prevalent condition of involuntary urine leakage resulting from faulty closure of the urethra typically associated with coughing, sneezing or exertion. SUI is often a debilitating and bothersome condition that can substantially reduce a woman's quality of life. Although non-surgical treatments such as pelvic floor exercises and behavioral modification are helpful in alleviating symptoms in some women [1], many proceed with surgery which is a more effective treatment [2].

In July 2011, the U.S. Food and Drug Administration (FDA) released a white paper [3] and safety communication [4] on the safety and effectiveness of transvaginal placement of surgical mesh specifically for pelvic organ prolapse. In addition, lawyers have publicly advertised their services, targeting women with transvaginal mesh placed for both pelvic organ prolapse and stress urinary incontinence (SUI), and the media has reported on the pelvic organ prolapse mesh litigation. We are concerned that the multimedia attention has resulted in confusion, fear, and an unbalanced negative perception regarding the midurethral sling as a treatment for SUI. This negative perception of the MUS is not shared by the medical community and the overwhelming majority of women who have been satisfied with their MUS. Furthermore, the FDA website states that: "The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year."[5]**.**

Justification for the Position Statement
1. Polypropylene material is safe and effective as a surgical implant.

Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh). As an isolated thread, polypropylene is a widely used and durable suture material employed in a broad range of sizes and applications. As a knitted material, polypropylene mesh is the consensus graft material for augmenting hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery. [6, 7] As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years [8].

2. The monofilament polypropylene mesh MUS is the most extensively studied anti-incontinence procedure in history.

A broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of the MUS as a treatment for SUI [9]. There are greater than 2000 publications in the scientific literature describing the MUS in the treatment of SUI. These studies include the highest level of scientific evidence in the peer reviewed scientific literature [9]. The MUS has been studied in virtually all types of patients, with and without comorbidities, and all types of SUI. Multiple randomized, controlled trials comparing types of MUS procedures, as well as comparing the MUS to other established non-mesh SUI procedures, have consistently demonstrated its clinical effectiveness [9-12] and patient satisfaction [12]. Among historical SUI procedures, the MUS has been studied as

long in follow-up after implantation as any other procedure and has demonstrated superior safety and efficacy [8]. No other surgical treatment for SUI before or since has been subject to such extensive investigation.

3. Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for our patients.

Since the publication of numerous level one randomized comparative trials, the MUS has become the most common surgical procedure for the treatment of SUI in the US and the developed world. This procedure has essentially replaced open and transvaginal suspension surgeries for uncomplicated SUI. There have been over 100 surgical procedures developed for the management of SUI and there is now adequate evidence that the MUS is associated with less pain, shorter hospitalization, faster return to usual activities, and reduced costs as compared to historic options that have been used to treat SUI over the past century. Full-length midurethral slings, both retropubic and transobturator, have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard for stress incontinence surgery [13]. Over 3 million MUS have been placed worldwide and a recent survey indicates that these procedures are used by > 99% of AUGS members [14].

4. The FDA has clearly stated that the polypropylene MUS is safe and effective in the treatment of SUI.

The midurethral sling was not the subject of the 2011 FDA Safety Communication, "*Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Vaginal Placement for Pelvic Organ Prolapse*."[3]. In this document, it was explicitly stated: "The FDA continues to evaluate the effects of using surgical mesh for the treatment of SUI and will report about that usage at a later date." In 2013, the FDA website stated clearly that: "The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year." [5]

Conclusion

The polypropylene midurethral sling has helped millions of women with SUI regain control of their lives by undergoing a simple outpatient procedure that allows them to return to daily life very quickly. With its acknowledged safety and efficacy it has created an environment for a much larger number of women to have access to treatment. In the past, concerns over failure and invasiveness of surgery caused a substantial percent of incontinent women to live without treatment. One of the unintended consequences of this polypropylene mesh controversy has been to keep women from receiving any treatment for SUI. This procedure is probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of our organizations which are dedicated to improving the lives of women with urinary incontinence.

On March 24, 2014, AUGS and SUFU posted two related documents, one concerning Frequently Asked Questions by Patients: Mid-urethral slings for Stress Urinary Incontinence and another for Providers.[129] The statements read, in part:

> "The mid-urethral sling is considered safe and effective by the US Food and Drug Administration (FDA). As with any surgery, complications can occur but they are typically minor and can usually be repaired."
>
> "A broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of mid-urethral slings as a treatment for SUI [1]."
>
> "The difficulties and complications associated with mid-urethral slings are similar in character to that seen with non-mesh procedures (bladder outlet obstruction, urinary tract injury, dyspareunia, pain, etc.) with the exception of vaginal mesh exposure and mesh perforations into the urinary tract."
>
> "As an implant for the surgical treatment of SUI, macroporous, monofilament polypropylene has demonstrated long-term durability, safety, and efficacy for up to 17 years [5]."
>
> "Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants."

F. The Royal Australian and New Zealand College of Obstetricians and Gynecologists (RANZCOG) Statement

In March 2014 RANZCOG published a position statement on midurethral slings.[130] The statement reads:

> "Mid-urethral slings are minimally invasive procedures developed in the early 1990s to treat female stress urinary incontinence. These slings are narrow, synthetic polypropylene tapes that are surgically placed beneath the middle part of the urethra (water pipe) to provide dynamic support to stop leakage from the bladder. They have been shown to be as effective as more invasive traditional surgery with major advantages of shorter operating and admission times, and a quicker return to normal activities, together with lower rates of complications.[3] This has resulted in MUS becoming the operation of choice in Europe, the United Kingdom, Australasia[4] and the USA[5] for treatment of SUI.
>
> The USA Food and Drug Administration (FDA) released a white paper[6] and safety communications[7] regarding safety and effectiveness of transvaginal placement of surgical mesh specifically for pelvic organ prolapse. A prolapse is where some of the pelvic organs bulge downwards giving rise to symptoms of an uncomfortable vaginal lump. Media attention[8] on this totally distinct and separate issue of mesh use in women has the potential to cause

[129] Id.
[130] www.ranzcog.edu.au.

> unnecessary confusion and fear in women considering MUS for treatment of stress urinary incontinence. Both RANZCOG and UGSA wish to strongly emphasise that the US FDA publications clearly state that MUS were not the subject of their safety communication.
>
> There is robust evidence[9-11] to support the use of MUS from over 2,000 publications making this treatment the most extensively reviewed and evaluated procedure for female stress urinary incontinence now in use. These scientific publications studied all types of patients, including those with co-morbidities such as prolapse, obesity and other types of bladder dysfunction. It is, however, acknowledged that any operation can cause complications and for MUS, these include bleeding, damage to the bladder and voiding difficulties[12]. Nevertheless, the results of a recent large multi-centre trial[13] have again confirmed the excellent outcomes and low risks of complications to be expected after treatment with MUS. Additionally, long term effectiveness has been demonstrated in studies following patients for up to 17 years.[14-15] In Australia, it has been the operation of choice to treat for female SUI since 2004. RANZCOG and UGSA support the use of monofilament polypropylene mid-urethral sling for surgical treatment of female stress urinary incontinence."

G. November 2015 ACOG/AUGS Practice Bulletin

A November 2015 ACOG/AUGS Practice Bulleting states the following regarding midurethral slings:[131]

> Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings. Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings.
>
> There are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women.
>
> ...

[131] Number 155, November 2015.

Synthetic midurethral mesh slings are the most common primary surgical treatment for stress urinary incontinence in women (67). Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension (68–70). Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings (68). Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings (69). For these reasons, midurethral synthetic mesh slings have become the primary surgical treatment for stress urinary incontinence in women (67, 71). However, in women who decline or are not candidates for synthetic mesh slings, autologous fascial bladder neck slings and Burch colposuspension (laparoscopic or open) remain effective treatment options.

Although controversy exists about the role of synthetic mesh used in the vaginal repair of pelvic organ prolapse, there are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women. For this reason, and to clarify uncertainty for patients and practitioners, the American Urogynecologic Society and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction published a position statement recognizing polypropylene mesh midurethral slings as the "standard of care" in the surgical treatment of stress urinary incontinence (72).

Although there are many ways to place midurethral slings, the main approaches used are retropubic and transobturator techniques. Evidence from a 2015 systematic review demonstrates that these approaches are effective and appear to be comparable in terms of efficacy and patient satisfaction (73). Subjective cure rates up to 1 year after surgery were similar and ranged from 62% to 98% (transobturator route) and 71% to 97% (retropubic route). Short-term objective and long-term (more than 5 years) subjective and objective cure rates also were similar. Voiding dysfunction, bladder perforation, major vascular or visceral injury, and operative blood loss were more common with retropubic slings, whereas groin pain was more common with transobturator slings. Mesh complications (eg, exposures, erosions) were uncommon and did not differ between routes of sling placement (2% overall).

Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings. Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings.

There are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women.

VI. Opinions

In forming my opinions, I employed methodologies consistently used by health care companies and regulatory authorities to address and evaluate premarket data, post-approval safety data, risk reduction strategies and labeling obligations. These methods are also consistent with those utilized by me, the sole member of Ulatowski Consulting, LLC, in the conduct of my assignments with both U.S. and international health care clients manufacturing medical devices including preparation of regulatory submissions and post-market efforts, preparation of regulatory and scientific protocols, labeling and other risk mitigation evaluations. My opinions are also predicated upon the Food, Drug, and Cosmetic Act, my numerous interactions with the Federal Trade Commission on device labeling and promotion, the Code of Federal Regulations, Federal Registers, and industry practices and standards.

My participation in this litigation and the development of the opinions enclosed herein follow an extensive review process. As described earlier, I possess extensive experience in the medical device industry and draw on this experience in conducting my tasks under the auspices of Ulatowski Consulting, LLC, including the reviews provided herein.

As described, I have performed a thorough and integrated review of the publicly available information and regulatory documents, including those produced during discovery, identified in this report and listed in Exhibit B. I analyzed those documents for their relevance. The employed methodology also included a review of the production documents, depositions/transcripts, and other materials provided to me by Counsel, or requested by me from Counsel. Upon retrieval, receipt, and review I considered documents for possible inclusion in the evaluation for this report. If additional relevant proprietary documentation was required, and I was unable to independently locate this data/information, I made a request of Counsel for any related documents to be reviewed by me. I analyzed these documents for their regulatory relevance and conformity to industry practices and standards in forming my opinions in the same manner I would have assessed them when I was a premarket evaluator or the chief medical device compliance officer at FDA, and also in the same way I would evaluate them in my

current capacity as a consultant to companies on medical device regulatory aspects.

The employed methods also include my reviews of depositions, corresponding exhibits, potentially associated with regulatory affairs, post-market surveillance, device design and manufacturing, and medical services, among others. Reviews of depositions and exhibits are critical. Because I have been engaged in all the aspects of medical device design, development and commercialization, I can interpret and evaluate industry testimony.

Based upon my analysis of these documents and information, as well as my experience, knowledge, and training, I have formed opinions with regard to the Ethicon TVT-O. Each of the opinions set forth below is held to a reasonable degree of scientific and regulatory certainty. My prior testimony is listed in Exhibit C. I have no publications in the past 10 years.

I may use visual aids or demonstrative exhibits, such as diagrams, images, slides or charts, to illustrate and or explain my opinions and analyses in this report, as well as excerpts, charts, and other information from the materials I have cited in my report or identified in the materials reviewed.

I reserve the right to supplement this report and my opinions as discovery progresses in this case.

1. It is my opinion that the recall of the Microvasive ProteGen Sling, one of the predicates for the TVT Classic, had no regulatory or safety impact whatsoever on the continued marketing of TVT-O. It was reasonable and proper and consistent with industry standards and practices for Ethicon to use ProteGen as a predicate.

The cleared 510(k) for the Ethicon Tension Free Vaginal Tape (TVT) System, also known as TVT Classic, included the ProteGen Sling, manufactured by Microvasive, a Boston Scientific Company, as one of the predicates for the Ethicon TVT Classic.[132] The Ethicon TVT System and the ProteGen Sling were similar in that they had the same intended use, clinical mechanism to achieve continence and insertion site, i.e., pubourethral sling to treat stress urinary incontinence by urethral support with incision on the anterior vaginal wall. They also used accessory devices and required anesthesia.

The Ethicon TVT System was different from the ProteGen Sling in several important respects. The material for the Ethicon TVT device is knitted filaments of polypropylene (Prolene) while the ProteGen Sling consisted of woven polyester impregnated with collagen. The collagen ingredient was absorbable. The Ethicon device utilized fixation through the skin while the ProteGen Sling used sutures anchored to bone.

FDA states the following regarding the ProteGen Sling in its Executive Summary to the Obstetrics and Gynecological Devices Advisory Committee

[132] ETH.MESH.00371539-00371542.

on September 9, 2011:[133]

> In 1996, the Surgical Fabrics (ProteGen Sling) device manufactured by Boston Scientific Corporation became the first pre-configured surgical mesh product cleared via the 510(k) pathway for surgical treatment of SUI. (The ProteGen Sling was cleared with an indication for "pubourethral support," a phrase which implies an indication for treatment of SUI.)

Boston Scientific/Microvasive reportedly recalled the ProteGen Sling in January 1999.[134]

Microvasive's voluntary recall of the ProteGen Sling, the sling predicate for the Ethicon TVT System, did not have a regulatory or safety impact on the Ethicon TVT System.[135] The safety impact is most important. In my opinion although the ProteGen Sling and the Ethicon TVT device were substantially equivalence by the FDA regulatory standard they were sufficiently different in materials and anchoring in the body to disassociate the ProteGen clinical experience from that of the Ethicon TVT Classic. Also, the post market clinical evidence for the Ethicon TVT Classic in January 1999 when the ProteGen Sling was recalled and later experience was demonstrating that the Ethicon TVT device was performing as intended.[136] The 510(k) for the Ethicon TVT System included clinical evidence attesting to its safety and effectiveness.[137] Therefore, there was no safety basis for a recall of the TVT device in January 1999.

Based on the lack of a safety issue, FDA would not have had a regulatory basis to take administrative action on the TVT Classic or the TVT-O 510(k)s. There is no explicit statutory authority or regulation on vacating a determination of substantial equivalence, or a regulatory method for FDA to rescind a 510(k) determination of substantial equivalence. However, a ruling of a US District Court gives credence to FDA's position that it has the authority to rescind a 510(k), albeit as the court opined in "rare situations" so long as FDA acts in a "reasonable time." [138,139]

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[133] FDA Executive Summary, http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/medicaldevices/medicaldevicesadvisorycommittee/obstetricsandgynecologydevices/ucm270402.pdf

[134] FDA public records of recalls do not extend to 1999. A statement of the status of ProteGen is contained in various publications, e.g., Erosion of Woven Polyester Pubourethral Sling, December 1999, http://www.ncbi.nlm.nih.gov/pubmed/10569572.

[135] ETH.MESH.00371496-00371497.

[136] Dr. David Robinson, a medical director at Ethicon, began using the TVT device shortly after it became available. He testified, "Eventually the TVT became the gold standard." Robinson deposition, 7/24/13, Page 45:10-11.

[137] Id., TVT System 510(k).

[138] FDA has considered a future statutory amendment to provide authority for rescission. See "Plan of Action for Implementation of 510(k) and Science Recommendations", http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhreports/ucm239450.pdf.

[139] Ivy Sports Medicine, LLC v. Sebellius et al., No 11-cv-1006.

FDA has employed an administrative procedure for rescission but the criterion for rescission by this administrative procedure when the ProteGen was recalled was not applicable to the Ethicon TVT System. Based on my experience, the criterion for rescission at that time was a finding that the applicant submitted incorrect information. An FDA administrative process for rescission of a 510(k) was in a proposed rule that never went final.[140] The expanded rescission criteria in the proposed rule were "information in the 510(k) is incorrect, incomplete, unreliable, or not evaluated properly by FDA in accordance with section 513(f) and (i) of the act." I conclude from my review of the Ethicon TVT System 510(k)[141] that none of these expanded criteria applied to the Ethicon 510(k).

FDA took no public action to rescind any sling device that relied on the ProteGen Sling as a predicate. FDA did not use any other statutory and regulatory remedy at its disposal to remove any Ethicon TVT device from the marketplace due to the recall of the ProteGen Sling. Indeed, FDA cleared several additional Ethicon slings after the ProteGen recall, including, for example, TVT-AA, TVT-O, TVT-Secur, TVT Abbrevo and TVT Exact (see Section IV.B. above for 510(k) listing).

It was reasonable and proper and consistent with industry standards for Ethicon to use ProteGen as a predicate when it submitted a 510(k) for TVT Classic. When Ethicon submitted the TVT Classic 510(k) ProteGen was a legally marketed sling with the same intended use as TVT Classic. It is industry practice to rely on similar products and ProteGen was a sling but not identical product.

2. It is my opinion that the PROLENE polypropylene material used in the Ethicon TVT devices including TVT-O has demonstrated long-term safe and effective performance that supports its continued acceptance as an implantable material. FDA continues to reaffirm its confidence in the safety and effectiveness of PROLENE. It was reasonable and proper and consistent with industry standards and practices for Ethicon to utilize PROLENE in various surgical products.

Plaintiffs' complaints and reports of their experts allege that PROLENE is biologically incompatible with human tissue. The allegation refers to shrinkage, bacteria, and chemical composition risks and cites a few selected references.[142] I believe, based on the regulatory and clinical history of PROLENE containing devices, that FDA and the medical community consider PROLENE containing devices, and therefore PROLENE to be clinically acceptable.

The assessment of risks is much more complex than just stating there are risks. There are risks with all implantable materials. Risks can be calculated and mitigated. Residual risks after mitigations, even if significant, can be acceptable based on a benefit/risk assessment. The final value of a device and its materials is based on this process.[143]

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[140] 66 FR 3523, 3525 (January 16, 2001).
[141] TVT System 510(k), K974098, ETH.MESH.00371496-00371594.
[142] In contrast to the few citations in the petition, a PubMed search reveals 5555 published papers using the search term "PROLENE."
[143] See ISO 14971, Risk Management standard.

PROLENE is the primary component in many FDA-cleared Ethicon products including, for example, sutures, mesh, and TVT devices like the TVT-O[144]. PROLENE is not a new material. PROLENE Polypropylene Suture (Nonabsorbable Surgical Suture USP, Type B) was first regulated by FDA as a drug prior to the enactment of the 1976 medical device amendments to the Federal Food, Drug and Cosmetic Act. FDA approved a New Drug Application (NDA), NDA 16-374, for Ethicon PROLENE Suture (monofilamentous dyed and undyed) over 45 years ago on April 16, 1969.[145] An order approving a new drug is a determination that the drug is safe and effective.[146] The approval for sutures in 1969 made of PROLENE stated the following:[147]

We have completed the review of this application as amended and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

The Investigational New Drug application supporting the PROLENE NDA included an assessment of the safety of PROLENE. Studies were conducted evaluating tissue reactions to PROLENE in the rat, rabbit and dog.[148] The full reports were submitted in the NDA as well as other preclinical data.[149] The NDA included extensive clinical data, consisting of numerous investigators and subjects.

The NDA file for the Ethicon PROLENE Suture and subsequent submissions, consisting of supplements, amendments and annual reports, is extensive.[150] Based upon my 37 plus years of experience at FDA and then consulting, I find the PROLENE suture NDA file to be a comprehensive compilation of medical and scientific evidence supporting the safety and effectiveness of PROLENE since it was marketed in 1969. The information submitted to FDA over the years not only meets the NDA requirements it is also consistent with industry standards and best practices for NDA submissions.

The NDA for PROLENE Suture was transferred from the Center for Drug Evaluation and Research to the Center for Devices and Radiological Health. Ethicon continued to comply with NDA/PMA reporting requirements until those NDA/PMA requirements were transformed to 510(k) requirements by the FDA reclassification of nonabsorbable polypropylene surgical sutures from Class III to Class II.[151]

Besides the approved NDA discussed above, FDA had a major opportunity to assess the safety and effectiveness of PROLENE when it classified surgical mesh. When FDA proposed the classification of the preamendments surgical mesh in 1982[152] it considered the recommendations of the General and Plastic Surgery, Orthopedic, and Gastroenterology

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[144] Comparison of TVT Classic to TVT-O, ETH.MESH.08108658.
[145] ETH.MESH.09625731-09625737. An NDA for a drug is an equivalent submission to a Premarket Approval application for a device.
[146] 21 U.S.C. §355.
[147] ETH.MESH.09625731.
[148] ETH.MESH.09626043.
[149] ETH.MESH.09626242-09626359.
[150] Original submission January 17, 1966 supported by IND 1688, 4 original volumes ETH.MESH.00019840-00019846. Subsequent submissions to FDA comprise nearly 50 primary volumes.
[151] ETH.MESH.09634662-09634663.
[152] 47 FR 2810 (January 19, 1982.

and Urology Device Panels. In classifying surgical mesh the Panels relied upon their clinical experience with mesh, their review of published clinical data, and their assessment of the risks posed by mesh to health as stipulated in the act regarding classification procedures.[153] FDA finalized the classification of surgical mesh, which now includes TVT devices, into Class II in 1988.[154]

Classification of the mesh by FDA into Class II established that under the law reasonable assurance of safety and effectiveness of surgical mesh would be based upon general controls, including, for example, 510(k) submissions, and any special controls FDA may finalize for the mesh.

I find no evidence in the litigation production, or on FDA's web site of any enforcement action taken by FDA against any PROLENE device or of any recall with a root cause related to the safety or effectiveness of its PROLENE material composition.[155]

Mr. Gregory R. Jones, Director of Regulatory Affairs when the TVT Classic was first marketed, testified regarding the 510(k) submission of TVT to FDA:[156]

> "PROLENE mesh is well-known, well understood, been on the market for quite some time. PROLENE sutures had been on the market and well-known and well understood. The testing that had been done over the years on PROLENE Suture and PROLENE Mesh was pretty extensive."

The clinical community is supportive of PROLENE as an implantable material. The January 3, 2014 AUGS-SUFU statement noted in Section V of this report states the following:

> "Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh). As an isolated thread, polypropylene is a widely used and durable suture material employed in a broad range of sizes and applications. As a knitted material, polypropylene mesh is the consensus graft material for augmenting hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery. [6, 7] As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years."

The March 24, 2014 AUGS/SUFU statement noted in Section V of this report states the following:

> "As an implant for the surgical treatment of SUI, macroporous,

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[153] 21 USC §360c(b)-(d).
[154] 53 FR 23856 (June 24, 1988).
[155] Recall activities included, for example, instances of counterfeit sutures and delamination reported within limited lots of PROCEED mesh.
[156] Gregory R. Jones deposition, August 20, 2013, Page 185:19-25.

> monofilament polypropylene has demonstrated long-term durability, safety, and efficacy for up to 17 years [5]."
>
> "Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants."

The table I constructed in Section III of this report lists numerous 510(k)s for Ethicon TVTs and mesh devices constructed of PROLENE polypropylene material. Every time FDA cleared one of these TVT or mesh devices it reaffirmed the safety and effectiveness of PROLENE. FDA cannot clear a device it considers to be adulterated or misbranded.[157]

FDA maintains knowledge of the performance of devices on the market. FDA has posted information regarding TVT on the FDA web and it held a public hearing on TVT in 2011 as noted earlier in this report. There were no concerns regarding PROLENE raised at the open public hearing of the FDA advisory committee by any individual. I am not aware of any petition filed with FDA to remove any PROLENE containing devices from the market. FDA continues to clear TVT devices made of PROLENE, such as the TVT Exact in 2013.

It is evident that FDA and the clinical community believe that the benefits of PROLENE outweigh its risks. The FDA and the medical community's pronouncements I note above in this report make it clear that PROLENE is clinically acceptable as an implantable material and products consisting of PROLENE are reasonably safe and effective for their intended use.

Given PROLENE's long safe and effective history as a material of implanted devices, and the lack of any FDA action to limit its use in devices, it was reasonable and proper and consistent with industry standards and practices for Ethicon to use PROLENE as the material for the TVT-O device.

3. It is my opinion that a change by Ethicon in mesh material or PROLENE weave specifications for TVT-O would require the submission of a new 510(k) to FDA and clearance by FDA before the modified device could be marketed. This opinion is based on FDA regulations and guidance and is consistent with industry standards and practices.

The composition of TVT-O mesh, as described in the original Ethicon TVT-O 510(k) K033568, cleared by FDA on December 8, 2003, is "knitted filaments of polypropylene (unpigmented and pigmented blue) PROLENE."[158] TVT Classic, K974098, is one of the predicates for TVT-O.[159] The 510(k) for the TVT Classic states the composition of the mesh is "knitted filaments of extended polypropylene identical in composition to that used in PROLENE polypropylene suture (Ref. NDA/PMA #16-374)."[160] Ethicon also stated to FDA that the polypropylene strands used to fabricate PROLENE mesh are the same strands used to fabricate PROLENE

[157] 21 CFR §807.100(b)(3).
[158] ETH.MESH.08108658.
[159] ETH.MESH.08108654.
[160] ETH.MESH.00371539.

polypropylene Nonabsorbable Surgical Suture.[161]

Dan Smith, currently an engineering fellow at Ethicon, testified that since the clearance of TVT Classic one clear PROLENE fiber in the mesh construction was replaced with a blue PROLENE fiber.[162] He also testified that there was no standard for mesh pore sizes and the mesh construction is measured or defined in courses and wales per inch, not pore size.

Experts for Plaintiffs proffer opinions that the TVT Classic design and material presented safety and effectiveness concerns and Ethicon should have considered alternative materials and designs.[163] Dr. Rosenzweig has opined that PROLENE was not suitable for TVT-O and failed to modify it. Dr. Iakovlev has discussed an alternative material called PVDF.

The experts for Plaintiffs do not state whether any of the changes they proffer would be subject to FDA clearance of a new 510(k). The fact is that a new material or significant specifications changes to PROLENE described by Plaintiffs experts would have required a new 510(k).

I assessed the proffered changes as I did for 25 years as a premarket submission evaluator using FDA regulations and related guidance as a basis for my assessment. The FDA regulation for 510(k) submissions, 21 CFR Part 807, requires a new 510(k) be submitted for a marketed device as follows:[164]

> (3) The device is one that the person currently has in commercial distribution or is reintroducing into commercial distribution, but that is about to be significantly changed or modified in design, components, method of manufacture, or intended use. The following constitute significant changes or modifications that require a premarket notification:
> (i) A change or modification in the device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process.
> (ii) A major change or modification in the intended use of the device.

FDA guidance provides direction to the industry on the types of changes to an existing device cleared under a 510(k) that may be significant.[165] The guidance states the following:

> **Will the material of the affected part of the implant be likely to contact body tissues or fluids?** Changes in materials that contact body tissues or fluids may critically affect the device's safety or effectiveness, either because of potentially new interactions of the device material on the body or because of the

[161] ETH.MESH.08476244.
[162] Smith deposition, 2/3/14, Pages 721:19-24 and 727:22-25.
[163] Expert Reports 4/24/15, Bruce Rosenzweig, MD and Dr. Vladimir Iakovlev.
[164] 21 CFR §807.81(a)(3).
[165] Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm.

> body's environmental effects on the new material in the device. Manufacturers should submit a new 510(k) for a change in implant material where the material contacts tissue (including bone tissue) or body fluid.

In addition to the above recommendation by FDA the decision flowcharts in the guidance make it clear that a material change or formulation change, e.g., a weave change, to an implanted device leads to a new 510(k). In addition, Ethicon would be required to verify and validate the changes to the TVT-O as required by the quality system regulation.

Some changes to the TVT-O PROLENE material would not require a new 510(k). Each changed should be preceded by an assessment by Ethicon of the regulatory impact of the change. A change in color of the PROLENE strands, laser cutting or minor changes in the manufacturing process such as those listed in a deposition testimony exhibit[166] would not require a new 510(k) but would require consideration by Ethicon of the need for verifications and revalidation per the quality system regulation.

According to regulations, manufacturers decide whether a change in a device is significant and needs FDA clearance. It is an industry standard and practice to rely on FDA's guidance on changes to 510(k)s to support their decisions. It is a standard practice for the decisions and basis to be documented and retained in design control records. Evidence shows that Ethicon followed these industry practices and would have done so when considering material changes to TVT-O.

4. It is my opinion that there has been no reason for FDA to recommend labeling changes to TVT-O. FDA requested changes to labeling for TVT Classic, the predicate for TVT-O, before clearance, but not to TVT-O. Ethicon modified TVT-O labeling voluntarily reflecting current thinking on the risks and benefits of transvaginal slings. This is reasonable and proper and consistent with industry standards and practices.

The salutation in the FDA Public Health Notification (PHN) issued October 20, 2008 on gynecological mesh is “Dear Healthcare Practitioner.”[167] It advises physicians regarding training and technique and notably provides three imperatives to physicians to inform patients about risks with mesh devices. There is no FDA recommendation in the PHN directed to manufacturers.

The July 13, 2011, update to the PHN was only for transvaginal placement of surgical mesh for treatment of pelvic organ prolapse. A 2013 update to the FDA web site regarding mesh for the treatment of SUI includes information to health care providers and patients. There are no recommendations for manufacturers. Physicians are advised to inform their patients of the risk of using mesh for SUI. Likewise, patients are advised to “ask your surgeon about all SUI treatment options, including non-surgical options and surgical options that do and do not use mesh slings. It is important for you to understand why your surgeon may be recommending a particular treatment option to treat your SUI.

[166] ETH.MESH.10633520.
[167] ETH.MESH.02252640-02252642.

Any surgery for SUI may put you at risk for complications, including additional surgery… Ask your surgeon the following questions before you decide to have SUI surgery…"[168]

FDA never recommended any labeling change to TVT Classic or TVT-O after clearance. FDA requested some labeling changes to TVT Classic labeling prior to the 1998 clearance including revision to the Indications for Use, Warnings, Adverse Effects, and Instructions for Use. Ethicon revised the labeling as requested to FDA's satisfaction.[169]

There is no law or regulation allowing FDA to require a labeling change for a cleared 510(k) device unless the labeling violates the law or regulations. FDA can request a change to labeling and it is industry practice to comply with such requests. Based on the public record FDA has never found that TVT-O cleared labeling violates the law or regulations. Based on the public health notices and FDA's pronouncements I reference above there was no reason for FDA to request a labeling change.

Despite the absence of any FDA regulatory directive for Ethicon to change the labeling for TVT-O Ethicon proactively and voluntarily issued updated Instruction for Use (IFUs) and patient brochures reflecting FDA current thinking on risks and benefits of transvaginal slings expressed in the updated 2013 public health notice.[170]

It is an industry practice for manufacturers to rely on FDA's current thinking when formulating labeling. FDA current thinking is expressed in documents such as recent labeling for similar devices and public health notices. It was reasonable and proper for Ethicon to revise its labeling after FDA published its updated PHN in 2013.

5. It is my opinion the FDA October 2008 Public Health Notice and 2013 updated FDA PHN for health care workers and patients on treatment of SUI support Ethicon's position that the patient brochures were intended as only part of the interaction between the physician and patient regarding the potential treatment options for SUI and the warnings, precautions, and adverse effects for each option. It was reasonable and proper and consistent with industry standards for Ethicon to view its brochures as supplemental to physician interaction.

Manufacturers may provide patient brochures as part of the labeling for their devices. FDA can require patient brochures for a Class II device, as a special control. There is currently no such requirement for TVT devices.

A patient brochure is not intended as a comprehensive and stand-alone expression of all risks and benefits of a device. It is information to be provided to the patient to assist in the communication between a patient and her doctor.

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[168] Information for Health Care Providers and Patients for SUI, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh.
[169] ETH.MESH.08476217-30.
[170] See opinion 11 for labeling.

The government describes informed consent as follows:[171]

> It is very important to realize that courts have increasingly held that informed consent is **a process**, not just a piece of paper.

The government describes the consent process, based on ethical principles, as follows:[172]

> You have the right to help decide what medical care is best for you. By law, your health care providers must explain your health condition and treatment choices to you.
> Informed consent means:
> - You are informed: you have received information about your health condition and treatment options.
> - You understand your health condition and treatment options.
> - You are able to decide what health care treatment you want to receive and give your consent to receive it.
>
> To obtain your informed consent, your health care provider may talk with you about the treatment. Then you will read a description of it and sign a form. This is written informed consent.
> Or, your health care provider may explain a treatment to you. They will ask if you agree to have the treatment. Not all medical treatments require written informed consent.

The testimony of Ethicon Medical Directors and others describe the role the patient brochures play in the informed consent process between the patient and her doctor. Dr. Charlotte Owens, a Medical Director at Ethicon, testified regarding patient labeling:[173]

> "I think that one of the main things we have to do when we're speaking directly to patients, because they're – we're delivering products that come through physicians, is there's a lot of information to encourage them to have a conversation about this with their physician…you can convey general statements that initiate a conversation between the patient and their doctor to determine what's the best step."

Susan Lin, a regulatory manager at Ethicon, testified:[174]

> "So it is the doctor's responsibility to communicate the risk to the patient before implant[ing] this device."

Dr. Piet Hinoul, a Medical Director at Ethicon testified:[175]

> "We make patient brochures available to facilitate the conversation between her and her doctor to come up with the right decision for her treatment."

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[171] http://www.ihs.gov/riskmanagement/index.cfm?module=part06.
[172] Informed Consent, http://www.nlm.nih.gov/medlineplus/ency/patientinstructions/000445.htm.
[173] Charlotte Owens deposition, June 20, 2013, Page 341:1-10.
[174] Susan Lin deposition, August 1, 2013, Page 1051:2-4.
[175] Piet Hinoul, MD. PhD, deposition, June 27, 1013, Page 407:3-6.

The FDA October 2008 PHN described above in Section III.B. supports Ethicon's belief is that the patient brochure is not the total sum and substance of informed consent. The PHNs clearly describe FDA's expectation that doctors provide the patient a written copy of the manufacturer's labeling and discuss options and risks with the devices and techniques. The 2013 FDA web information on SUI notes that physicians should provide the patient the patient brochure or labeling, if available, and make sure the patient understands the risks and complications.

In these pronouncements FDA does not say the brochure labeling stands on its own as the sole source of information to the patient. Patient labeling is only one element of a process described by FDA. The doctor is the key intermediary and source of information between the patient and use of a device.

Although manufacturers of transvaginal slings are not required to provide patient brochures it was reasonable and proper as an industry standard and practice for Ethicon to do so voluntarily for its transvaginal slings. Industry standards direct that brochures provide introductory information to the patient who then receives compete information from her doctor during the consent process. FDA's PHN's aid the patient in making communication with her doctor more informative.

6. It is my opinion there are no regulatory requirements regarding the patient brochures including the TVT-O brochure. The brochures are not false or misleading. The brochures are consistent with industry standards and practices.

The medical device labeling regulation, 21 CFR Part 801, does not contain any requirement for patient labeling for a prescription medical device or requirements concerning the content of patient labeling. A manufacturer may voluntarily choose to provide patient labeling in consideration of industry practice for similar devices.[176]

Patient labeling for prescription devices, e.g., brochures or videos, if provided, are subject to the misbranding provisions of the act. Also, if patient labeling is provided then 21 CFR §801.109(d) of the device prescription labeling regulation may be interpreted to include the need for attachment of an IFU to patient labeling. FDA has not enforced this provision. It is a common industry practice to attached an IFU to patient labeling.

FDA has published guidance concerning device patient labeling but FDA guidance is voluntary for manufacturers and statements in guidance are recommendations or suggestions unless what is stated is a regulatory requirement.[177] The FDA device patient labeling guidance notes "*This*

[176] A PMA approval may require labeling as a condition of approval, or a regulation may require patient labeling for a specific device. Neither of these apply to TVT.

[177] Guidance on Medical Device Patient Labeling, http://www.fda.gov/MedicalDevices/DeviceRegulationand Guidance/GuidanceDocuments/ucm070782.htm.

document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations."

Patient labeling may describe risks and benefits of the device. The concept of "fair balance" between risks and benefits statements in labeling is a consideration for manufacturers. FDA is not prescriptive on this issue for medical devices. There is no medical device statutory or regulatory provision concerning "fair balance" in prescription or over-the-counter device labeling or advertising.[178] There is such a provision in drug regulations but it is unenforceable for devices.[179]

Given the above regulatory and best practice considerations I have examined the TVT-O patient brochures listed in Table 1.

TABLE 1 Patient Brochures For Ethicon Slings Including TVT-O

Brochure	Bates	IFU Attached	Information Included (examples)
What You Can Do About It…	ETH.MESH.08003181-08003196	yes	Incontinence description, talk to doctor, treatment options, risks, benefits, refer to IFU…
Breaking the Ice About SUI	ETH.MESH.01613143-01613146	yes	Ditto
What You Can Do About It…	ETH.MESH.08003197-08003212	yes	Ditto
Ditto	ETH.MESH.00658421-00658429	yes	Ditto
Find Out How to Stop Urine Leakage Like Bonnie Did	ETH.MESH.03458123-03458138	yes	Ditto
Ditto	ETH.MESH.08003247-08003262	yes	Ditto
Ditto	ETH.MESH.03459088-03459104	yes	Ditto
One day…End of Story	ETH.MESH.08003263-08003278	yes	Ditto
Find out…Like Bonnie Did	ETH.MESH.08003215-08003230	Partial w refer	Ditto
Ask Yourself	ETH.MESH.06087471-06087472	yes	This is a "Help Seeking" brochure
Ditto	ETH.MESH.08003231-08003246	yes	Ditto
Stop Coping. Start Living.	ETH.MESH.08003279-08003294	yes	Ditto
Ditto	ETH.MESH.09744840-09744845	yes	Ditto
Ditto	ETH.MESH.09744848-	yes	Ditto

[178] There are advertising provisions for restricted devices in 502(q) and (r) of the act but TVT-O is not a restricted device.
[179] 21 CFR Part 202, Prescription Drug Advertising.

	09744855		
Ditto	ETH.MESH.09744858-09744863	yes	Ditto
Ditto	ETH.MESH.08003303-08003313	yes	Ditto
TVT-Obturator	ETH.MESH.09744870-09744871	yes	Help seeking

In general, in all the patient brochures the patient is advised to talk to her doctor about her condition, the treatment options, and the risks and benefits. This is consistent with the 2008 and 2013 FDA Public Health Notice instructions regarding communication between doctors and patients on treatment of SUI, as detailed in Section IV of this report.[180]

The risk section of the brochures accurately states that all surgical procedures present risks. Risks are listed in all brochures and the patient is referred to the IFU information for a complete description of risks. The patient is informed to talk with her doctor about the risks. Again, this communication between doctor and patient is consistent with the FDA PHN instructions to doctors and patients concerning treatment of SUI.

The potential or claimed benefits of TVT are discussed in the brochures. The dates of the brochures range from 2001 to 2011. I would expect this information contained in the brochures to change over time.

There are bases for the claims in the patient brochures. The claim of reduced operative time is reasonable when compared to the operative time for open surgical procedures and that sling procedures are generally out patient procedures as noted by FDA. The claims of long-term safety and effectiveness are supported by clinical data, testimony, and by professional organization opinions detailed in Sections V.

Ethicon patient brochures state, for example, "my doctor explained there is a minimally-invasive, simple treatment called TVT."[181] FDA statements to its Advisory Panel and by professional organizations in Sections IV and V of this report, and deposition testimony, support Ethicon's claim of TVT's minimal invasiveness.

TVT-O is within a group of products designated by FDA as 1st generation slings. In the September 9, 2010 presentation to the Obstetrics and Gynecology Devices Panel, FDA describes the 1st generation suburethral slings as "minimally-invasive."[182]

The AUGS statement I describe in Section V of this report states "Developed in the early 1990's, midurethral slings (MUS) treat stress urinary incontinence (SUI) in a minimally invasive, generally outpatient procedure."

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[180] See reference to other TVT brochures in II.F.5. of this report.
[181] ETH.MESH.01613143-46.
[182] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM272113.pdf, pages 45 and 47.

Dr. Martin Weisberg describes TVT and its minimal invasiveness in the following testimony:

> "Do you believe that the term "minimally invasive" is an accurate way to describe Gynecare TVT-O?
> THE WITNESS: Yes. It was similar (to TVT Classic or retropubic) in that there were two skin incisions and one urethral incision."[183]

The brochures and video are compliant with the device labeling regulations and there is no basis to find them false or misleading.

The brochures are also consistent with industry standards and practices. The brochures contain the important recommendation for the patient to speak with her doctor about her treatment options and best course of action. The brochures reasonably include risks and benefits information that can be expanded upon in the communication between the patient and her doctor.

7. It is my opinion that there is no evidence that the TVT-O device was inadequately manufactured including that it failed to meet specifications.

There is no testimony or litigation production evidence, or public information I have attesting to a manufacturing nonconformity of TVT-O.[184]

I requested and was provided by counsel a record of recalls for the TVT devices. There was one recall in 2000 for the TVT Classic due to needle pull off from the tape.[185] In my opinion and based on MDR reports the physician can visually detect this type of malfunction during surgery.

My review of the FDA Warning Letter database on January 29, 2016 revealed no Warning Letters to Ethicon related to Ethicon TVT devices.[186] FDA may issue a Warning letters to a manufacturer if it determines, typically based on inspection observations, that there are violations of FDA law and regulations.

My review of TVT-O Issue Reports (See opinion 9) include product related complaints that meet the FDA definition of malfunctions. According to Ethicon complaint procedures (See opinion 8) Ethicon must investigate these events and trend events. Complaint trends may identify manufacturing nonconformities that require corrective and preventive action. I did not identify any records of CAPAs for Gynecare TVT-O related to manufacturing defects in the time period associated with this litigation.

8. In my opinion Ethicon was proactive in striving to ensure that its complaint and medical device reporting procedures, training of staff on

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[183] Weisberg deposition, 8/9/13, Page 985:2-8.
[184] A nonconformity is the nonfulfillment of a specified requirement per 21 CFR §820.3(q).
[185] ETH.MESH.00108420-00108423.
[186] FDA Warning Letter database, http://www.fda.gov/ICECI/EnforcementActions/WarningLetters.

those procedures, and implementation of those procedures were substantially compliant with regulations. The procedures and Ethicon's activities were also reasonable and proper and consistent industry standards and practices.

Device manufacturers must establish and maintain a quality system that is appropriate for the medical device they design and manufacture. Also, each manufacturer shall establish quality system procedures and instructions.[187]

It is important to first examine the Ethicon complaint and device reporting procedures to determine if Ethicon procedures were compliant with FDA regulations, which is the scope of this opinion, and then to examine whether Ethicon implemented those procedures properly, which is the scope of the next opinion.

In my experience the examination of manufacturing procedures may reveal occasional procedural or documentation aberrations. This is not extraordinary considering the vast extent and complexity of a quality system record system for a company like Ethicon. The standard I applied in reviewing quality records while at FDA and now as a consultant is whether there the records demonstrate a fundamental lack of appreciation and adherence to regulatory requirements and a pattern of noncompliance.

Franchise Work Instructions for Summary and Individual Medical Device Reporting, PR551-006/Rev.33,[188] describes the reporting and processing of Product Complaints to comply with 21 CFR Section 803, Medical Device Report (MDR) requirements. According to Ethicon, this procedure was in effect during the time of the implant of the Plaintiff. Revisions 25-33 are noted in this version. The definitions are consistent with the FDA MDR regulation as is the process flow for MDR reporting. It includes summary decision trees including the elements of death and serious injury and malfunction related aspects, and whether the event may be related to the device. It includes consideration whether there is information or medical rationale that states the device did not cause or contribute to a death. It includes aspects not in the MDR regulation but company specified steps such as treatment of litigation files, sutures, and packaging.

The Franchise Procedure for Summary and Individual Medical Device Reporting, PR551-06, revision 30, noted above as a prior revision of Rev.33[189] provides detailed procedures for MDR decision-making.

Franchise Policy for Product Complaint Management, PL0000087 undated[190], states, “it outlines the required elements for all complaints relating to ETHICON franchise products to ensure compliance to J&J policy, regulatory requirements, and voluntary standards.” It is a high level document and describes the general regulatory elements for complaint and MDR processes. It does not address CAPA except in terms of

[187] 21 CFR §820.20(e).
[188] ETH.MESH.09804784-803.
[189] ETH.MESH.03589458-03589480.
[190] ETH.MESH.03743182-03743193.

escalation to CAPA. It is the first revision of the policy[191] put in place in 2010.

A version of the Franchise Complaint Procedure, PR-0000118, version 18,[192] put in effect in 2011 provides details on elements of the complaint process described in the above policy. Some of the key elements include certain definitions such as adverse event and incident, minimum information required in a complaint file, complaint investigation, design history review, medical review, serious injuries, deaths and/or incidents. In regard to medical review the procedure states for 5.2.8."(Medical) Review may be requested to help in determination of device relationship to reported event, to determination of severity of an event for purposes of adverse event reporting."[193] Section 5.2.11.4 states "Medical Assessment: For the reported event, the WCQ Medical Director will write a medical assessment based on the reported complaint information and include one of the following conclusions in the investigation comments (refer to Appendix V for definitions):

- The Device Caused Event
- The Device Contributed to Event
- The Device Potentially Contributed to Event
- The Device Not Likely Related to Event
- The Device is Not Related to Event
- Not Enough Information to Draw a Conclusion

If the Medical Assessment concludes that the device Caused, Contributed to or Potentially Contributed to the Event, then the medical assessment should also include commentary on whether or not the resultant harm is an anticipated outcome of the device or that the outcome is noted in the labeling."

The August 8, 2013 deposition of Mark C. Yale, manager of worldwide customer quality for Ethicon for a period of time, addresses Ethicon's complaint process. Mr. Yale testified on the content of the Ethicon Franchise Instructions for Summary and Individual Medical Device Reporting, PR551-006 Rev.31, 7 Sept 2012.[194]

In deposition testimony Mr. Yale described the Ethicon complaint handling process including the capture of complaints, the source of complaints, the investigation of complaints, reporting of complaints, as necessary, batch record review, and medical review of complaints.[195] He stated there were operating procedures for complaint management and MDRs.[196] He described the process called PQI (product quality issue) used to escalate a signal or trend to management for assessment and appropriate action.[197] He also described the corrective and preventive action (CAPA) process in general. In my opinion he accurately described the purpose of CAPA stating, "So it's sort of core to the quality system in the big picture from the perspective on how you take and improve things." and also "So the PQI process is clearly proactive."[198]In

[191] Dan Lamont deposition, 05/24/2012, Page 485:4-7.
[192] ETH.MESH.03743365-03743387.
[193] Lamont testified that this was in place since 2006, Lamont deposition, 05/24/2012, Page 492:3-4.
[194] ETH.MESH.07277675-07277696.
[195] Mark E. Yale deposition, 8/8/2013, Page 492:5-493:18.
[196] Id. Page 494:4-11.
[197] Id. Page 497:9-24.
[198] Id. Page 499:9-500:17.

my opinion all these processes address the requirements for complaint handling and CAPA under the FDA Quality System regulation.

Mr. Yale testified further on the use of medical offices in the process of determining whether complaints were reportable. He states:

> "medical directors help us make that final decision of…would it require…intervention to prevent permanent impairment."[199]

He also states in regard to the MDR procedure on reportability

> "…medical rationale…its coming from a medical director"[200]

The complaint and MDR procedures meet the requirements of 21 CFR Parts 820 and 803, and industry standards and best practices, in that the processing of complaints and MDR multi-step reporting decision process includes all the key elements in the regulation such as death or serious injury, intervention, and malfunction determinations. The process includes some Ethicon-specific steps such as steps 4a-4d of revision 31. These variations are permitted by the MDR regulation and typically a practice of industry.

An Ethicon internal audit of quality system aspects including complaint, MDR and CAPA procedures in 2002, according to Mr. Yale[201] includes observations related to documentation, the need for some clarity in procedures, a few procedural lapses. Internal audits are a requirement of the quality system regulation, 21 CFR §820.22 and an industry best practice to help ensure the quality system is in compliance and for continuous improvement purposes. FDA does not inspect these audit reports or any CAPAs initiated due to these audits in order to encourage self-improvement by a company.

Deposition records indicate that Ethicon is committed to proper training of staff and compliance with reporting requirements as evidenced by several staff emails.[202]

In the deposition testimony of Mark Yale, three events are discussed, along with the conclusions of Charlotte Owens, the Medical Director at that time.[203] Not being a clinician I cannot render a medical opinion about her conclusions but note that her input into event causation and her conclusions are permitted according to the MDR regulation under 21 CFR §803.20(c)(2). In any event, two of these events were reported to FDA as MDRs as noted in Mr. Yale's deposition testimony.[204] One was not reported as an MDR based on Medical Director assessment I note above.

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[199] ETH.MESH.03575123, 03575101, Mark E. Yale deposition, 8/7/2013, Page 72:15-18.
[200] Id. Page 84:12.
[201] Mark Yale deposition, 8/7/13, Page 151:11.
[202] ETH.MESH.01949198-01949200, ETH.MESH.03531443-03531448, ETH.MESH.01814250-01814252, ETH.MESH.00318881-00318889, ETH.MESH.00874613-00874615, ETH.MESH.06496130-06946134.
[203] ETH.MESH.03575123, ETH.MESH.03575101, ETH.MESH.03575054.
[204] Mark E. Yale deposition, 8/8/2013, Page 549:19-556:22.

FDA inspected Ethicon between August 9, 2005 and September 8, 2005 and the inspector listed one observation in a Form 483[205] issued to Ethicon at the end of the inspection. The observation stated that there was no documentation regarding determinations during complaint processing whether devices failed to meet specifications.[206] FDA issued no Warning Letter as a result of the inspection and therefore Ethicon was not cited for any violations as a result of this inspection. Nevertheless, Ethicon took voluntary action and responded to the observation in a timely and thorough manner.[207] FDA issued no final agency determination of a violation.

In sum, I find the Ethicon procedures I examined to be substantially compliant with FDA regulations. The procedures and Ethicon's related practices were also consistent with industry practices and standards. The procedures include the methodologies manufacturers regularly employ in receiving, analyzing and investigating complaints. The methodologies include identification of complaints that must be reported to FDA. It is standard practice for complaint staff to rely on medical experts to decide whether a device may have caused or contributed to a clinical event.

9. It is my opinion that the TVT-O Issue Reports and the associated MedWatch reports are indicative of Ethicon's substantial compliance with complaint and MDR regulatory requirements. They also indicate Ethicon's decisions were reasonable and proper and consistent with industry standards and practices.

I examined Issue and Medwatch (MDR) Reports for Ethicon Gynecare TVT-O. Several reports are before the treatment of Plaintiff in September 2010 but evaluation of all reports is important to assess Ethicon's attention to its postmarket obligations. The reports are as follows:

DEVICE	TYPE DOC	YEARS	TOTAL PAGES	ETH.MESH START
TVT O	Issue Report	2004-2012	5545 pages	02658063 2012 02652710 2004 02652985 2005 02653814 2006 02654866 2007 02655451 2008 02655902 2009 02656482 2010 02657205 2011
TVT O	Medwatch	2005-2012	1794 pages	03578068 Bates not in consecutive order
TVT O	FDA web	2012-2015	numerous	no bates

[205] A Form 483 lists FDA inspector observations. Observations are not an FDA final determination regarding compliance.
[206] ETH.MESH.00319683.
[207] ETH.MESH.00330769-00330775. ETH.MESH.00319665-00319672. ETH.MESH.04095019-04095026.

	site			

A single Ethicon internal Issue Report is approximately 8 pages while a single Medwatch Report to FDA is 2 or 3 pages for the FDA Medwatch Form 3500A.

I have the following observations from my review of these reports:

1. Ethicon Issue Reports document complaints, their investigation by Ethicon, and Ethicon's decisions determining whether a complaint is reportable to FDA.

2. The Issue Reports document complaints concerning procedure and post procedure related events described in labeling.

3. The events noted in the MDRs, derived from the Issue Report events, are consistent with the adverse effects listed in labeling.

4. There are rare reports generally for TVT devices concerning shrinkage, tissue reaction and scarring.

5. Complaints for all TVT devices originate from a variety of sources, such as health care facilities, doctors, patients, journals, and salespersons.

6. Events not resulting in MDRs generally include those where there was no patient effect reported, the injury resolved without intervention or where the event was determined to be unrelated to the device.

I reviewed a Complaint Vigilance Audit Report dated February 2002[208] and an Independent MD&D Sector Audit of Ethicon MDR process in 2012.[209] As noted in opinion 7 these internal audits are required by regulation and are an industry best practice but are not inspected by FDA. The audits are part of the continuous improvement process in a company. The purpose of the audits is to identify quality system observations and areas for improvement. I agree with Catherine V. Beath who testified regarding these audits:[210]

> "I'm confident we had a plan to address them (the identified issues). You're always trying to improve."
>
> "But this (the 2012) audit basically said the reporting decisions are consistent with regulations and FDA guidance. The information and rationale to support a decision is sometimes inadequate."

She also testified:[211]

> "Based on a number of inspections that they (FDA) have done at the Somerville facility, almost always of the complaint MDR system, I think they're pretty confident that we follow the regulations and that when we find we have gaps, we correct them.

[208] ETH.MESH.02249640-642.
[209] ETH.MESH.07724068-080.
[210] Catherine Beath deposition, July 12, 2013, Pages, 561:23-24 and 569:4-7.
[211] Id. Page 576:23-577:5.

> As a matter of fact, they've told us that, that they have a lot of confidence in Ethicon to correct problems."

I believe Ethicon's reporting of events to FDA to be substantially compliant with FDA regulations. I base this on my review of the issue reports and Medwatch forms, the Ethicon internal audit reports, and FDA inspection of Ethicon's complaint and MDR procedures. The reports also provide ample evidence of Ethicon's adherence to industry standards and practices for documenting complaints, analyzing and investigating complaints, and reporting complaints to FDA according to its procedures.

10. It is my opinion that Ethicon substantially complied with FDA premarket and related quality system requirements and industry standards and practices prior to marketing the TVT-O devices; clinical information continues to support the safety and effectiveness of TVT-O.

I examined whether (1) ETHICON conducted adequate testing according to regulations and industry standards supported clearance of TVT-O and continued marketing of the device, and (2) whether TVT-O was ever found unsafe or ineffective. I can set aside (2) by stating the simple answer that FDA has never found TVT-O to be in violation of the laws and regulations it administers including violation of adulteration and misbranding prohibitions.

<u>The TVT-O 510(k) submission meets FDA requirements, industry standards and best practices</u>

In general, regulations require a new device to be cleared or approved by FDA, unless otherwise exempt from such requirements, before it can be marketed.[212] The TVT-O device was submitted in a Special 510(k). According to FDA, the Special 510(k) relies on manufacturer compliance with the design control requirements of the Quality System Regulation (21 CFR Part 820). A Special 510(k) and may be submitted for a modification to a manufacturer's own device that has been previously cleared under the 510(k) process. The TVT-O was a modification of the cleared Ethicon TVT Classic, TVT Blue and TVT-AA Guides.[213]

A Special 510(k) allows the manufacturer to declare conformance to design controls and requires only a summary of the testing, not the full reports of the data.[214]

I examined the TVT-O Special 510(k) for the information required to be submitted to FDA.[215] The Special 510(k) includes the following

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[212] 21 CFR §807.81 and 21 CFR §814.1.
[213] ETH.MESH.01818654.
[214] How to Prepare a Special 510(k), http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/premarketnotification510k/ucm134573.htm.
[215] How to Prepare a Special 510(k), http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomark

information:[216]

The information meets the regulatory requirements. The content of the TVT-O Special 510(k) follows the form and content as recommended by FDA in its Special 510(k) guidance and is consistent with industry standards and practices. Pages 8-10 of the 510(k) list the premarket verification tests conducted by Ethicon, the success criteria for the tests and the results.[217] The FDA evaluation of the 510(k) is properly documented.[218]I conclude that TVT-O is equivalent to TVT Classic and the

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etyourdevice/premarketsubmissions/premarketnotification510k/ucm134573.htm.

[216] ETH.MESH.08108850.

[217] Based on FOI 07004171.

[218] Id.

accessories are equivalent, based on intended use, descriptive characteristics vis-a-vis that of the predicates, and test data.

FDA has full access to all the design control documents used as the basis for the marketing of a device and for a Special 510(k). During the review of the 510(k) FDA can request a manufacturer to submit any design control information it may need to render a final decision. There is no record of FDA requesting additional design records during its review of the TVT-O submission.

Supportive evidence of the safety and effectiveness of TVT-O

An Ethicon Clinical Expert Report, the regulatory strategy for bringing the device to the market, the design risk analysis and design validation for TVT-O provide evidence of the safety and effectiveness of TVT-O.

The 16 December 2003 Gynecare TVT-O Clinical Expert/Evaluation Report by Dr. Martin Weisberg, a medical director at Ethicon, describes the "inside out" TVT procedure used by Professor de Laval, precautions and warnings, and a summary of the clinical experience with the "outside in" procedure and the inside out" procedure of Professor de Laval.[219] Dr. Weisberg describes de Laval's study comparing the trans-obturator approach to the traditional TVT abdominal approach. He also describes an ongoing clinical study by Dr. Jean Laval. Dr. Weisberg concludes:

The transobturator "inside-out" approach to implanting a polypropylene mesh results in the identical placement of the tape as in the "outside-in" procedure. This, coupled with the results of De Leval's "inside-out" study data, indicates that the efficacy is equivalent. Urethral injury is much less likely to occur with the "inside-out" approach because the passage of the guide and tape in the area of the urethra is performed under direct visualization. Logically, for the same reason, the "inside-out" technique will allow positioning of the tape at the mid urethra to be more accurate.

The "inside-out" transobturator technique therefore seems more precise than previous techniques, appears easy to perform, is reproducible, may not require cystoscopy, and is likely to results in fewer complications. The results in terms of curing incontinence seem to be equal to the techniques described previously in the short-term.

Based on the above, I am confident that the "inside-out" transobturator approach to implanting a polypropylene mesh for the treatment of stress urinary incontinence in females is safe and effective and that additional clinical studies are not necessary at this time.

The 7 July 2003 Regulatory Strategy by Sean O'Bryan, Senior Project Manager, Regulatory Affairs, describes the plan to design, manufacture and market the TVT-O device.[220] It contains a summary of the device and clinical information. It properly describes the regulatory pathway for the TVT-O in both the US and Europe.

[219] ETH.MESH.00222899-00222909.
[220] ETH>MESH.00222250-00222252.

The 19 December 2003 Device Design Safety Assessment (DDSA), Revision 1, for the TVT-O device components consists of a component descriptions, medical impact, a detailed qualitative & quantitative characteristics worksheet, a detailed use related hazards worksheet, a DDSA risk and hazards assessment form with criteria attached, and approval sheets.[221] Based on ISO 14971, Medical Devices - Application of risk management to medical devices, an FDA recognized standard for assessment of risk and a basis for industry risk management practices, the DDSA is consistent with the ISO standard.

The 19 December, 2003 design validation report for TVT-O, entitled "Final Report #03-0740, GYNCARE TVT Obturator System" documents the clinical validation of the TVT-O device using health care professionals to assess packaging and physicians to assess the product. The tested product was representative of initial production units, as permitted by FDA regulations. This type of validation is consistent with industry practices for implants and meets the FDA validation requirement for an actual or simulated clinical test before the device may be marketed.[222]

The report documents comments by the doctors in an initial study noting that comments were addressed in product design and/or documentation or were preferences or suggestions, not requirements. Ethicon assessed the results and concluded that although the results were satisfactory minor revisions of the training materials could emphasize technique differences. A subsequent study met expectations.

TVT-O Design History File

Exhibits 217, 223-228 of the May 15, 2013 deposition of Daniel J. Smith document the Design History File (DHF) for the TVT-O.[223] Mr. Smith testifies in detail regarding the content of this DHF.[224] According to FDA regulations, a DHF shall contain or reference the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of the quality system regulation.[225]

The TVT-O DHF is an extensive compilation of documents attesting to the rigorous and thorough design, testing and evaluation of the TVT-O by Ethicon. The DHF deposition exhibit record is comprised of 7 well-ordered books separating the DHF into somewhat equal numbers of pages. The DHF itself is structured into 7 parts as follows:

1.0: Product Documents
2.0: Regulatory Documents
3.0: Design Control Documents
4.0: Testing
5.0: Neuchatel (Final Assembly + Packaging)
6.0: JEB (Helical Passers + Winged Guide)
7.0: Mediline (Plastic Tube + Mesh Attachment)

The DHF is completely consistent with design control requirements of the quality system regulation and relevant industry standards and

[221] ETH.MESH.00222401-00222426.
[222] Validation, 21 CFR §820.30(g).
[223] Daniel J. Smith deposition, 5/15/13, exhibits 223-228.
[224] Id. Pages 85-155.
[225] 21 CFR §820.30(j).

practices as it contains details regarding all the required parts of design controls including design development planning, design inputs, design outputs, design reviews, design verification and validation and design transfer.

I note there are three DDSA's for the TVT-O components in the DHF entitled Versions 0-2.[226] The PROLENE material is contained in the prior TVT device and is not addressed in these DDSAs. Version 0 with cover memo dated December 9, 2003, Version 1 is a post-launch DDSA with cover memo dated August 30, 2004 (noted above in this section), and Version 2 is an update dated December 15, 2003. I also note the records I describe in part 8.b. are in the DHF.

Expert Opinions Conclude TVTs, including TVT-O, Continue to Be Safe and Effective

The findings by FDA and its advisory panel in 2011, the position statements of clinical professional associations and a clinical standard organization I detail in Sections IV and V of this report attest to the continued safety and effectiveness of TVT-O.

11. It is my opinion that the labeling for the TVT-O is substantially compliant with regulatory requirements, claims are adequately supported, and labeling meets industry standards and practices.

I examined the following Instructions for Use (IFUs) for TVT-O:

IFU Number	Bates ETH.MESH	Content Per Regulation	Date Range IFU Used
TVT-O IFU 2003/A	02340829-02340901	Indications, contraindications, warnings, precautions, adverse reactions, actions, how supplied, storage, instructions for use, Rx statement	1/7/04 - 3/4/05
2003/B	02340756-02340828	Ditto	3/7/05 - 5/19/05
2003/C	02340974-02341046	Ditto	5/25/05 - 4/29/08
2005/D	02341047-02341118	Ditto	4/23/08 - 5/7/2010
2005/E	02340902-02340973	Ditto	5/12/10 - current revision
2015	Ethicon web site	Ditto	currently posted

The labeling includes extensive instructions for use, and extensive warning and precautions. The Contraindications and Warnings for the IFUs prior to 2015 included the following information:

[226] ETH.MESH.00259416-00259501.

CONTRAINDICATIONS

As with any suspension surgery, this procedure should not be performed in pregnant patients. Additionally, because the PROLENE polypropylene mesh will not stretch significantly, it should not be performed in patients with future growth potential including women with plans for future pregnancy.

WARNINGS AND PRECAUTIONS

- Do not use GYNECARE TVT Obturator procedure for patients who are on anti-coagulation therapy.
- Do not use GYNECARE TVT Obturator procedure for patients who have a urinary tract infection.
- Users should be familiar with surgical technique for urethral suspensions and should be adequately trained in the GYNECARE TVT Obturator procedure before employing the GYNECARE TVT Obturator device.
- Acceptable surgical practice should be followed for the GYNECARE TVT Obturator procedure as well as for the management of contaminated or infected wounds.
- The GYNECARE TVT Obturator procedure should be performed with care to avoid large vessels, nerves, bladder and bowel. Attention to patient anatomy and correct passage of the device will minimize risks.
- Bleeding may occur post-operatively. Observe for any symptoms or signs before releasing the patient from hospital.
- Although bladder injury is unlikely to occur with this technique, cystoscopy may be performed at the discretion of the surgeon.
- Do not remove the plastic sheaths until the tape has been properly positioned.
- Ensure that the tape is placed with no tension under the mid-urethra.
- Do not perform this procedure if you think the surgical site may be infected or contaminated.
- Since no clinical information is available about pregnancy following sub-urethral sling procedure with the GYNECARE TVT Obturator System, the patient should be counseled that future pregnancies may negate the effects of the surgical procedure and the patient may again become incontinent.
- Since no clinical information is available about vaginal delivery following a sub-urethral sling procedure with the GYNECARE TVT Obturator System, in case of pregnancy delivery via cesarean section should be considered.

The adverse reactions section in all the above IFUs for the TVT-O prior to 2015 include the following:

ADVERSE REACTIONS

- Punctures or lacerations of vessels, nerves, bladder or bowel may occur during needle passage and may require surgical repair.
- Transitory local irritation at the wound site and a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation and inflammation.
- As with all foreign bodies, PROLENE mesh may potentiate an existing infection. The plastic sheath initially covering the PROLENE mesh is designed to minimize the risk of contamination.
- Over correction i.e. too much tension applied to the tape, may cause temporary or permanent lower urinary tract obstruction.

The 2015 labeling includes an expanded adverse reactions section.

All the IFUs meet the regulatory requirements for prescription labeling

in that all the IFUs have the required prescription labeling elements.[227]

I defer to the testimony of Ethicon Medical Directors' clinical opinions regarding the scope, content and interpretation of the listed adverse reactions.

Catherine V. Beath, VP QA/RA at Ethicon, testified regarding the role of the medical directors in deciding the content of labeling:[228]

> "…all of the medical directors that I knew that were in the business actually implanted these devices, they had done procedures, so they were the best experts to tell us when it would be appropriate for other physicians like them where the information would be useful."

Labeling statements for PROLENE containing devices have their origin in the NDA for PROLENE sutures. For example, FDA approved a 1988 label for the suture that included warnings related to "minimal, transient acute inflammatory reaction" that tracks with the TVT-O labeling.

In sum, the labeling meets the requirements of the labeling regulation. I do not believe labeling for implantable devices can describe all commonly understood general surgical risks. The labeling is not intended to be a textbook of gynecological surgery. The labeling notes the importance of use of TVT-O only by physicians trained in the treatment of stress urinary incontinence and specifically in implanting the TVT-O. In many respects training, mentorship and publication currency are more important than labeling since it is common knowledge that labeling is not the primary resource of information for a doctor concerning a device.

Industry standards prescribe the contents of device labeling and set forth various mandatory elements, which must be in a device label. This includes indications for use, warnings, and potential adverse events, among other information. Industry standards dictate that labeling cannot be false or misleading. Ethicon's labeling for TVT-O contained all of the elements and components required by industry standards, and it was neither false nor misleading in any of the information presented. It is my opinion that labeling for TVT-O conformed to industry standards and practices at all times.

12. It is my opinion that Ethicon's risk management policies, processes and procedures and documentation related to TVT-O were substantially compliant with regulations, guidance, and industry standards and practices.

The Quality System regulation requires manufacturers to conduct a risk analysis, where appropriate, as part of design validation.[229] There is no FDA requirement that manufacturers comply with ISO 14971, an international risk management standard, to use as a basis for the risk

[227] 21 CFR §801.109.
[228] Catherine V. Beath deposition, July 11, 2013, Page 198:19-24.
[229] 21 CFR §820.30(g).

analysis or to document in a risk report anything other than the risk analysis.

With that said, in my experience, virtually all device manufacturers, including Ethicon, voluntarily adopt a complete risk management program because risk management throughout the life cycle of a medical device has become an industry standard and best practice. A complete risk management program is required in order to market a device in many jurisdictions outside the USA such as Europe and Canada.

I examined several Ethicon risk management related records. Some are not specific to Gynecare TVT-O but are indicators to me of Ethicon's approach to risk management for all of its devices. The procedures are indicative of Ethicon's risk management process at the time of treatment of Plaintiff in 2010. The procedures include the following:

Franchise Procedure for Medical Device Risk Management Plan, PR602-003, Revision 20.[230] The process includes the standard elements of risk analysis, risk evaluation, risk control, residual risk evaluation, evaluation of production and postproduction information, and reassessment of risk as needed during the life cycle of the product.

Franchise Procedure for Post Market Surveillance, PR-0000385, Revision 5 (two versions).[231] This process is referenced in the Risk Management Procedure noted above. Daniel J. Lamont, director of postmarket surveillance, testified that these were not necessarily the final versions in the Ethicon system[232] but I believe they are at least relevant indictors of Ethicon's process. The PMS plan includes collection and assessment of postmarket signals from a variety of sources, risk categorization, escalation of issues as needed, and follow up.

Operating Procedure for Failure Modes and Effects Analysis Application (aFMEA) or Design (dFMEA), OP650-011, Revision 14.[233] The process includes determination of a risk priority number, assessing that RPN according to risk categories, taking action to reduce risk, when necessary, and reassessing the risk after action.

Device Design Safety Assessment (DDSA) Summary Report, TVT Obturator, December 2003, with a summary report of the medical impact and benefit, qualitative and quantitative characteristics with relevance and comments noting the response, hazard worksheet, assessment forms, criteria and assignment of risk level.[234]

DDSA Version 2, for components of the TVT Obturator describing the medical impact and benefit of the device and an assessment of the characteristics, whether the characteristic is applicable and a response is needed, and comments describing the response.[235]

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[230] ETH.MESH.03742413-439.
[231] ETH.MESH.06773111-130 and 06774005-030.
[232] Daniel J. Lamont, deposition April 3-4, 2013, Page 99:17-23 and 133:15-18.
[233] ETH.MESH.03742801-835.
[234] ETH.MESH.00222401-00222406.
[235] ETH.MESH.01808687-01808698.

Device Design Safety Assessment (DDSA) Re-evaluation for TVT, updates the DDSA completed by Medscand in 2000 for the TVT Classic. As noted, it assesses 11 hazards not identified in the 2000 DDSA, and reassesses a newly identified pull off hazard based on MDR reportable complaints and other complaint trends.[236]

Mr. Lamont, director of postmarket surveillance at Ethicon, provided clear and thorough deposition testimony regarding Ethicon's postmarket procedures. He stated, for example:

> So typically or historically the quality engineers would be responsible in that first…one year or two years post launch of a product. And they would assess whether the product was stable in the marketplace. So they would look at the complaints that were coming in and compare it against the risk profiles that they had worked on prior to launch and…acertain how the product was performing[237]
>
> Q: From a postmarketing surveillance point of view, when you are assessing the performance of the TVT family of products, what are the sources of information that you intake into the process?
>
> A: So complaints and adverse events. We would also look at internal NCRs…any CAPAs…if there are any products or issues we've had to escalate, we have a process called PQI…if we had any field actions…our medical affairs organization performs literature searches…if there was any sort of customer feedback…It could also include sources such as postmarket clinical trials that might be performed. It could include any type of benchtop testing…it could also include something like an independent postmarket trial.[238]

He states in regard to complaints: "So for the TVT family of products, generally speaking, we have very stable rates of complaints and adverse events reported."[239]

He also states, in regard to medical rationale for not reporting a complaint: "That would come between the analyst and likely Dr. Chen and the group. So that would—that determination itself wouldn't be done independently without medical."[240]

I find these procedures and reports are all consistent with ISO 14971, the standard used as the basis for industry risk manangement practices. All the elements of the standard are addressed in Ethicon's the risk management processes. The processes are substantially compliant with the FDA requirement for a risk analysis for each type of product. Mr. Lamont's testimony demonstrates a high degree of integration of risk management into Ethicon's operating procedures.

13. It is my opinion that FDA's evaluation of substantial equivalence in a 510(k) includes an analysis of the safety and effectiveness of the device.

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[236] Contained in TVT design history file ETH.MESH.01317508-613.
[237] Daniel J. Lamont deposition, 4/3/13, Page 52:13-23.
[238] Id. Page 69:6 to 70:10.
[239] Id. Page 211:17-19.
[240] Id. Page 274: 11-14.

The Amended Petition states that "No formal review of safety and effectiveness is required" in a 510(k).[241] I disagree.

In August 2010, an FDA 510(k) Working Group carefully assessed the 510(k) program and provided recommendations to senior FDA management.[242] The report states the following in regard to safety and effectiveness determinations in 510(k)s (emphasis added):

> With the exception of certain lower risk devices that are exempt from premarket review, CDRH reviews the safety and effectiveness of medical devices for their intended use prior to marketing. Under the premarket approval (PMA) process, each manufacturer must independently demonstrate reasonable assurance of the safety and effectiveness of its device for its intended use. Under the premarket notification (510(k)) process, CDRH will clear a new device if it finds, through review of a 510(k) submission, that the device is substantially equivalent to a predicate. Generally, predicate devices, as largely class II devices, are those for which there is a reasonable assurance of safety and effectiveness with general and applicable special controls.
>
> The 510(k) program, as it currently exists, is intended to support FDA's public health mission by meeting two important goals: making available to consumers devices that are safe and effective, and fostering innovation in the medical device industry.
>
> When a predicate has a well established risk/benefit profile and is generally well regarded by the healthcare community, a premarket comparison of a new device to that predicate, with sufficient information, can provide reasonable assurance that the device, subject to general and applicable special controls, is safe and effective for its intended use.

The determination of safety and effectiveness in both a PMA and a 510(k) is based on the statutory and regulatory standard of valid scientific evidence, as stated in regulations as follows (emphasis added):[243]

> (1) Although the manufacturer may submit any form of evidence to the Food and Drug Administration in an attempt to substantiate the safety and effectiveness of a device, the agency relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective. After considering the nature

[241] Amended Petition, page 4.
[242] CDRH Internal Preliminary Evaluations – Volume 1, 510(k) Working Group, Preliminary Report and Recommendations, http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsand Tobacco/CDRH/CDRHReports/UCM220784.pdf.
[243] 21 CFR §860.7(c)(1).

> of the device and the rules in this section, the Commissioner will determine whether the evidence submitted or otherwise available to the Commissioner is valid scientific evidence for the purpose of determining the safety or effectiveness of a particular device and whether the available evidence, when taken as a whole, is adequate to support a determination that there is reasonable assurance that the device is safe and effective for its conditions of use.
>
> (2) Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use.

The Act has been amended several times.[244] One such change was the Medical Device User Fee Act of 2002 (MUFMA).[245] According to FDA, MDUFMA was enacted "in order to provide the Food and Drug Administration (FDA) with the resources necessary to better review medical devices, to enact needed regulatory reforms so that medical device manufacturers can bring their safe and effective devices to the American people at an earlier time…"[246]

A guidance issued by FDA on the determination of substantial equivalence notes the following "The 510(k) review standard (substantial equivalence of a new device to a legally marketed (predicate device) differs from the PMA review standard (reasonable assurance of safety and effectiveness) in that the 510(k) review standard is comparative whereas the PMA standard relies on an independent demonstration of safety and effectiveness. Nonetheless, the principles of safety and effectiveness underlie the substantial equivalence determination in every 510(k) review."[247]

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[244] Amendments to the Federal Food, Drug and Cosmetic Act, http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/default.htm.

[245] PL 107-250 (Oct. 26, 2002).

[246] MDUFA, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109149.htm.

[247] Evaluating Substantial Equivalence in Premarket Notifications, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm404770.htm.

14. It is my opinion that the adverse press and litigious environment after the 2011 FDA Safety Notice resulted in an atypical surge of TVT MDR reports.

I describe in this report the FDA public health notices and the September 2011 meeting of the FDA Obstetrics and Gynecology Advisory Committee. The Committee discussed the benefits and risks of pelvic mesh and transvaginal tape. On July 13, 2011, FDA posted a Safety Communication of Pelvic Mesh for POP.

In my experience, and as I note below from FDA statements and the literature, those implanted with a TVT device (or who think they may have a TVT device) may become aware of FDA activity and publicity concerning TVT devices from various sources including, for example, their doctor or from the media, such as lawyer advertisements.[248] Patients may become concerned about the effect, if any, that the device has on their future welfare based on the media reports. Researchers note "Clinicians should be aware of the impact of these advertisements on patient opinion and counsel patients accordingly with unbiased and scientifically accurate information."[249]

During the period from 2011 onward there was considerable public information and media attention on pelvic mesh, including information FDA posted on its web site.[250] Koski's 2014 publication notes the following regarding transvaginal mesh:[251]

> Clinicians have encountered patients with heightened concern regarding the mesh. For example, it is currently not uncommon for patients several years out from a TVM procedure with no complications or symptoms to present questioning whether their mesh should be removed. Although there is a high value in patient awareness of these issues as well as in discussion between patients and physicians, information disseminated in a nonmedical environment and outside of the proper context could result in unnecessary patient anxiety or fear.

FDA believes that effective medical risk communication on matters of public health interest like pelvic mesh is important to inform doctors and assist them with patient care, and to also inform patients and to provide current recommendations and answer questions. At the patient follow up visits the doctor and the patient have the opportunity to discuss this information and the future course of clinical care. The doctor's ability to influence patients' decisions may be hampered when patients become aware of information on a device (that may be biased due to certain pecuniary interests) they may have been treated with

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[248] Michelle Elaine Koski et al, Patient Perception of Transvaginal Mesh and the Media, Urology 84:575-582.
[249] Id.
[250] Id. and 8/2/15 web search reveals 13,300 results using keywords "pelvic mesh lawsuits."
[251] Id.

before their doctor can inform them of accurate information and discuss it with them.

In its Strategic Plan for Risk Communication[252] FDA states "…the ultimate decision about whether to act on warning information (such as a recall notice) is made by an individual, taking into account the information received, his or her own knowledge, values, and, sometimes, consultation with a medical professional. But each person needs to receive and understand the information necessary to help inform choices.

FDA provides an illustration of challenges with implanted devices as follows:

Example 1: Implanted Devices

The Facts: Many American families have a member with an implanted device helping to keep a regular heartbeat. After years of experience with the device implanted in many people, the manufacturer learns that a small device piece may fail in an extremely small number of people. The manufacturer and FDA decide that devices that have not yet been implanted should be recalled. In most cases, the risks of removing the device outweigh the risks of leaving the device in, given the benefits of the device for the patient. How does communication ensure a successful recall of the remaining devices without causing undue concern for those with the device already implanted?

The Challenge: Some worried patients may make unnecessary office visits, and even potentially harmful decisions about removing a device that is providing a significant benefit—a benefit that outweighs the risk of device failure.

Effective risk communication: Effective risk communication achieves both of the desired ends—an effective recall and an informed patient—in a way that avoids patients making potentially costly and dangerous decisions. This generally means that a complex set of risk and benefit information must be communicated in a way that consumers will attend to, understand, and be able to apply to their individual situations.

In a paper on health care policy and regulatory[253] the authors state "Field actions taken by a manufacturer are often very expensive and come with an attendant amount of attention, publicity, and legal action. While this attention provides significant opportunities to inform physicians and patients, it often leads to fear and—sometimes—inappropriate actions." Physicians and patients may decide to remove devices that are functioning well.

FDA recognized the effect of litigation and other actions on reporting of medical device reports. In information provided to the Orthopedics Advisory Panel in 2012 FDA stated:[254]

> "Recalls, negative media attention, litigation, and increased/decreased usage of a medical device may substantially

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[252] Strategic Plan for Risk Communication, Urology, 84(3), 2014:575-582. http://www.fda.gov/aboutfda/reportsmanualsforms/reports/ucm183673.htm.

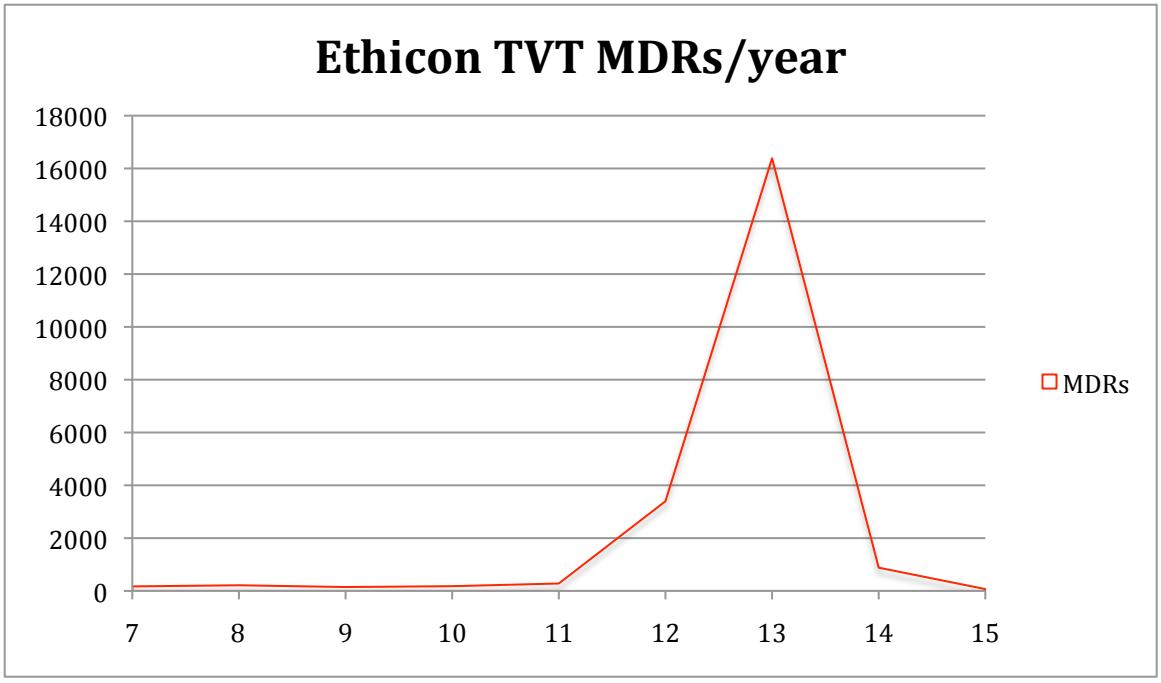
[253] Sharma, A, et. al., Health care policy and regulatory implications on medical device innovations: a cardiac rhythm medical device industry perspective, J Interv Card Electrophysiol. 2013 March; 36(2):107-117.

[254] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM309406.pdf.

> increase or decrease the number of MDRs received by the FDA. The recall for the DePuy ASR (August 23, 2010) contributed to the sharp increase in MoM THR MDRs received in 2010 and 2011. For example, of the 12,137 MoM THR reports received in 2011, DePuy ASR accounted for 9,006 of these reports (74.2%)."

In my experience in dealing with many instances of increased media concerning a device I can confirm the above statement that various media result in patient and physician responses that will affect clinical results and may result in increased medical device reports to FDA. In every meeting I had with manufacturers of implants associated with media attention the risk of unnecessary explants existed and immediate, effective risk communication necessary.

The following figure displays the atypical surge in TVT MDRs after the increase in media attention, e.g., lawyer ads, in 2011 concerning pelvic mesh. The trend of MDR submissions before 2011 was a slowly increasing straight line with fewer than 300 reports during 2011. I would have expected during the normal course of reporting that the established trend would continue. However, in 2012-2014, after the increase in media attention, the MDR reports increased 40 fold.[255] The vast majority of MDR reports during 2012-2014 are from attorneys while before 2011 the reports are from the manufacturer or from user facilities. In 2015 the MDRs submitted have returned to pre-2012 levels.



As I noted, companies and FDA attempt to reduce unnecessary explants through effective risk communication. The FDA has posted on its web

[255] MDR analysis conducted 9/30/15. MDRs include all Ethicon TVT devices.

site the following information regarding pelvic mesh implants to decrease unnecessary surgeries:[256]

- Continue with your annual and other routine check-ups and follow-up care. There is no need to take additional action if you are satisfied with your surgery and are not having complications or symptoms.

In sum, a surge in TVT MDRs occurred from 2011-2014 when media attention, e.g., legal advertisements, increased. This surge skews the probable true clinical risk profiles for the devices. As I note, the unbiased trend is reflected in the pre-2012 MDR submission statistics.

15. It is my opinion that the safety and effectiveness of laser cut mesh was properly verified according to regulations. Mechanically cut mesh continued to be reasonably safe and effective. Ethicon's addition of laser cut mesh was reasonable and proper and consistent with industry standards.

The FDA quality system regulation, 21 CFR Pat 820, requires that design changes to a device must be validated or where appropriate verified, reviewed, and approved before their implementation.

Ethicon produced TVT-O with either a mechanically cut or a laser cut edge. The mechanically cut edge was distributed first by Ethicon. Ethicon conducted Voice of Customer (VOC) interactions with doctors to learn of their views on laser cut mesh prior to its introduction.[257]

An Ethicon presentation in January 2005 reported that laser cut and mechanically cut mesh have the same physical attributes in regard to elongation, uniaxial tension, flexural modulus and pull-out force but structural integrity is different. The presentation describes a 2 week animal study where the two types of meshes maintained equal histological and mechanical properties.[258]

There are several verification tests reports verifying the safety and effectiveness of laser cut slings. Ethicon test reports compare the elongation, particle loss and rigidity of both meshes.[259] There are design verifications of laser cut mesh sheath removal.[260] A biocompatibility report states "This base material is intrinsically safe and without significant effects...This, the clinical use of laser-cut GYNECARE TVT PROLENE mesh implant is not expected to result in sny adverse biocompatibility effects for patients."[261] Ethicon conducted a particle loss with a test report dated 3/9/06.[262]

A risk management report of TVT laser cut mesh assessed the potential harms, their severity and estimated frequency, and determined that a

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[256] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm345205.htm.

[257] ETH.MESH.06878438-39.

[258] ETH.MESH.00442129-

[259] ETH.MESH.01320328-33, 021614610-24 and 06696367-79.

[260] ETH.MESH.00309290-301 and 00309314-31.

[261] ETH.MESH.04939001

[262] ETH.MESH.00309332-50.

risk benefit analysis was not needed.[263] Ethicon assessed complaints for laser cut mesh to support the laser cut mesh risk management plan.[264]

There are three clinical expert reports pertaining to laser cut mesh. The first dated 2/28/06 by Drs. Weisberg and Robinson is for TVT Secur and concludes, "It is not anticipated that there will be any clinical differences in the devices that utilize laser cut mesh."[265] The second dated 3/7/06 is for TVT Classic, TVT-O and TVT-A concludes "The physical properties that might affect clinical performance are essentially the same...Clinical data is not necessary to establish the safety and effectiveness of the devices affected by these changes."[266] The third report dated 4/18/06 applies to the same devices.[267]

Ethicon documented a change notice for laser cut mesh indicating the completion of a new design matrix and the need for new quality plan and device master record. The change notice concludes that a new submission to FDA is not needed.

Ethicon continued to market mechanical and laser cut mesh to meet customer preferences.

Ethicon verified the laser cut mesh as evidenced by the tests and analyses noted above. These tests and analyses and the changes indicated on the change notice are consistent with industry standards and practices.

Expert Reports for Plaintiffs

I reserve the right to more specifically respond to the opinions of Drs. Pence and Parisian, and to amend my opinions pending further discovery.

[263] ETH.MESH.00223779-84.
[264] ETH.MESH.01784779-82.
[265] ETH.MESH.01189423-39.
[266] ETH.MESH.01784823-28.
[267] ETH.MESH.00309275-78.

Executed in Herndon, Virginia on February 24, 2016.

Timothy A. Ulatowski

APPENDIX A: CV for Timothy A. Ulatowski

Timothy A. Ulatowski

[redacted]

Independent Consultant

Ulatowski Consulting LLC

Extensive Regulatory Experience ~ Risk Management ~ Technical Expert

A unique medical device consultant with extensive experience in both premarket evaluation of new medical devices and enforcement of FDA laws and regulations. Over 36 years of significant public health achievements, creating major regulatory programs and policies, developing and implementing strategic and risk management plans, and building collaborations with global regulatory partners and industry. Proven skills in advising industry on regulatory issues, assessing compliance and enforcement actions, evaluating premarket documents, managing and supervising large organizations, resolving complex technical and scientific problems of individual firms to those of national and international scope, and communicating to diverse audiences.

Selection of Notable Accomplishments

Hands on technical leadership of numerous compliance, enforcement and recall actions, many of national and global importance

Initiated use of novel corporate enforcement actions

Created effective internal quality management system used as a model program in FDA

Lead author of international guidance documents on aspects of the Global Harmonization Task Force medical device regulatory model

Recognized in “Top 100” of medical device professionals/MDDI

Primary reviewer of hundreds of Premarket Notifications, Investigational Device Exemptions, Premarket Approval Applications, recalls and compliance actions

Leader of team that developed the current FDA device standards program

Author of many key FDA premarket guidance documents, technical standards and publications

FDA key witness in federal court (US v Abtox), contributor to many court cases, advisor to DOJ and FDA criminal investigations office

Lead for agency on many GAO, OMB and Congressional activities

FDA spokesperson to major press and to large audiences

HHS Team Leader and technical expert remediating Anthrax contamination of Senate and Postal Service buildings

Creator of FDA/CDC/EPA tripartite collaborations on chemical germicides and co-author of current FDA/EPA national regulatory scheme for chemical germicides

Co-author and collaborator on sharps injury prevention guidance, related OSHA and NIOSH regulations and policies, resulting in documented reduction of injuries

Recipient of numerous major FDA awards

Professional Experience

Ulatowski Consulting LLC: Member

April 2014- Present

Independent consultant on FDA regulatory matters

NSF Health Sciences (formerly Becker & Associates Consulting Inc.): Vice President, Regulatory and Compliance

September 2011 – April 2014

- Ensure effective and timely solutions to a variety of FDA regulatory and legal issues
- Provide expert advice and recommendations on premarket, quality systems, compliance and device reporting
- Train industry executives and staff on FDA requirements

NDA Partners LLC: Principal

January 2011 – June 2012

- Advise clients on FDA regulations and law regarding product submissions, compliance and enforcement actions, and postmarket surveillance activities
- Serve as an expert witness in litigation
- Conduct due diligence

FDA, CDRH: Director, Office of Compliance and Senior Advisor for Enforcement

January 2003 – January 2011

- Managed and supervised office of four divisions and 180 professional staff responsible for ensuring compliance with medical device laws and regulations
- Directed FDA device quality system and bioresearch enforcement programs
- Directed inspection assignments and assessed quality system and bioresearch monitoring inspection reports and company/investigator/sponsor/IRB responses to determine violations
- Worked with all FDA districts, ORA and drug, biologics and food compliance executives to formulate enforcement strategies and actions
- Hands on evaluation and management of recalls, device advertising and promotion, MDRs, registration and listing, and medical device field resource allocation and prioritization
- Created new device enforcement policies and programs, directed implementation of the Commissioner's strategic action items, and participated in executive strategic planning at the agency and center levels
- Co-leader of FDA Medical Device Field Committee, an ORA/CDRH collaboration
- Initiated comprehensive training program for compliance staff and web-based information for the public
- Co-leader of 2010 user fee legislation post market committee, devising proposals and strategies with key Center and Agency staff for next round of legislation
- Senior Device Enforcement Advisor September 2010 – January 2011

FDA, CDRH: Head of USA Delegation, Global Harmonization Task Force and FDA representative to GHTF Study Group 1 Premarket

January 1995 - October 2010

- Managed the activities of the USA FDA participants to the GHTF Steering Committee and the five study groups; collaborated with USA industry task force members, USA leader on the GHTF Steering Committee for last four years
- Coordinated creation and review of documents and recommended agency decisions on pending documents to Center Director
- Primary author of several GHTF documents, including the original premarket “STED” document, and Global Model document, which are now used internationally
- Frequently trained international government staff on GHTF and FDA procedures

FDA, CDRH/Office of Device Evaluation: Director, Division of Dental, Anesthesiology, General Hospital, and Infection Control Devices

December 1996 – January 2003

- Managed premarket activities, such as review of premarket submissions and investigational applications, panel meetings, guidance development, and collaborative support for other CDRH offices
- Led development of the division during a major reorganization
- FDA lead on numerous international standards committees, reengineering task groups, and interagency task forces dealing with significant public health issues
- Succeeded in reducing review times while improving the quality and rigor of reviews
- Primary reviewer on numerous 510(k)s, IDEs, and PMAs
- Agency and ISO technical expert on medical device sterilization and disinfection

Prior FDA experience, short summary

Device Evaluation Associate Director, Branch Chief and front line 510(k), IDE, and PMA reviewer

Director, Investigational Device Staff, IDE application review and protocol advice

New Drug Evaluation Product Manager, NDA and IND activities and advisory committee exec sec

Microbiologist, National Center for Antibiotic Analysis, drug assessments

Prior to college and FDA career: US Army 1968 – 1971

Education

- Master of Science/Physiology with Biomedical Engineering emphasis, 1988 GPA 4.0

Georgetown University School of Medicine

- Bachelor of Science/Microbiology, 1974 cum laude

Pennsylvania State University

APPENDIX B: Testimony

Depositions:

University of Pittsburgh of the Commonwealth System of Higher Education d/b/a University of Pittsburgh v. Varian Medical Systems, Inc.

Civil Action No.: 2:08-cv-01307 (USDC, Western District of Pennsylvania)

David M. Kloss, et al, v. I-Flow Corporation, et al, Case No. 2:10-cv-00295-JFC (USDC, Western District of Pennsylvania)

Retractable Technologies, Inc. and Thomas Shaw v. Becton, Dickinson and Company, Civil Action No.2:08-cv-16 (Folsom) (USDC, Eastern District of Texas Marshall Division)

Diagnostic Devices Inc, v. Pharma Supply, Inc. et al, Diagnostic Devices Inc, v. Taidoc Technology Corporation, Case No.3:08-CV-00149-MOC-DCK (USDC, Western District of North Carolina, Charlotte Division)

Brenda F. Kitrosser v. Nuvasive, Inc. et al., Case No: 37-2009-00099700-CU-MM-CTL [Consolidated with Case No: 37-2010-00099400-CU-PO-CTL] (Superior Court of the State of California In and For the County of San Diego, Central Branch)

Superior Court of New Jersey, Law Division, Atlantic County

In re Pelvic Mesh/ Gynecare Litigation, Case No.291 CT, Master Case 6341-10

Jackson, et al v DePuy Orthopedics, No. CAL 10-32147 (Prince George's County, MD)

Strum v. DePuy Orthopaedics, Inc., et al., No. 11 L 009352 (Circuit Court, Cook County, Illinois)

Dorney-Madgitz v. DePuy Orthopedics, Inc., et al., 5:11-cv-001240-RBS (USDC, Eastern District of Pennsylvania)

Weinstat, et al. v. Dentsply International, et al., San Francisco Superior Court No. CGC-04-432370

Braun v. Medtronic Sofamor Danek, USDC, District of Utah, Central Division, Case 2:10-cv-01283

Connie Schubert and Kevin Schubert v. Ethicon, Inc., Ethicon Women's Health and Urology, a division of Ethicon, Inc., Gynecare, and Johnson and Johnson, et. al., In the Circuit Court of Jasper County, Missouri at Joplin, Case No. 10AO-CC00219

Sekisui America Corporation and Sekisui Medical Co., Ltd. v. Richard Hart and Mary Louise Trudel-Hart, USDC, Southern District of New York, Case 1:12-cv-03479-SAS (for Plaintiff)

Carol Lewis and Kenneth Lewis v. Ethicon, USDC, Southern District of West Virginia, MDL No. 2327

April Christine Cabana v. Medtronic Inc. (et al), Superior Court of the State of California, County of Los Angeles, Case No. BC 465 313

Christine Napolitano v. Synthes, Inc., USDC, District of Connecticut, Civil Action 3:09-CV-00828

Herlihy-Paoli v. DePuy Orthopedics, Inc., et al, 3:12-CV-04975-K (USDC, Northern District of Texas, Dallas Division)

City of Lakeland Employees Pension Plan v. Baxter International Inc., No. 10-cv-6016, USDC, Northern District of Illinois

Smith v. Baxano, Inc. et al, Superior Court of Washington for Snohomish County, Case No. 13-2-02714-1

Andrea Smith v DePuy Orthopedics, et al., District Court of Tulsa County, Oklahoma, No. CJ-2011-05804

Zimmer NexGen Knee Implant Products Liability Litigation, USDC, Northern District of Illinois, Eastern Division, MDL No. 2272, Master Docket No.:1:11-cv-05468

Sandra Garcia v Rodolfo J. Walss, MD, Johnson & Johnson, Inc. and Ethicon, Inc., District Court, 103rd Judicial District, Cameron County, Texas, Cause No. 2013-DCL-3511-D

Laura Ness v Depuy Orthopedics, Inc., et al., In the Circuit Court for Baltimore City, Case No. : 24-C-14-002465

Consolidated Fresenius Cases, Commonwealth of Massachusetts, Middlesex SS., Superior Court Department of the Trial Court, Civil Action No. 2013-03400-O Session

Aoki, Christopher, Greer, Klusmann, Peterson, Thibodeau (separate Plaintiffs) v DePuy Orthopedics, Inc. et al,. USDC, Northern District of Texas, Dallas Division, MDL No. 2244

Center City Periodontists, P.C., et al. v. Dentsply International, Inc., Eastern District of Pennsylvania, Civil Action No. 10-00744.

Michael Parker, Individually and Amy Parker, Individually v. Veronica A. Vasicke, MD; Bluegrass Orthopedics & Hand Care, PSC; and I-Flow Corporation, Fayette Circuit Court, Eighth Division, Civil Action No. 12-CI-3543.

Court Testimony:

Strum v. DePuy Orthopaedics, Inc., et al., No. 11 L 009352 (Circuit Court, Cook County, Illinois)

Brenda F. Kitrosser v. Nuvasive, Inc. et al., Case No: 37-2009-00099700-CU-MM-CTL [Consolidated with Case No: 37-2010-00099400-CU-PO-CTL] (Superior Court of the State of California In and For the County of San Diego, Central Branch)

Weinstat, et al. v. Dentsply International, et al., San Francisco Superior Court No. CGC-04-432370

Sekisui America Corporation and Sekisui Medical Co., Ltd. v. Richard Hart and Mary Louise Trudel-Hart, USDC, Southern District of New York, Case 1:12-cv-03479-SAS

Becky S. Anderson v. Medtronic, Inc. (et al), Superior Court for the State of Washington, County of King, No. 12-2-17928-0 SEA

Donald Gustafson v. Zimmer, Inc., District Court, Collin County, Texas, 366th Judicial District, Cause No. 366-03111-2011

Herlihy-Paoli v. DePuy Orthopedics, Inc., et al, 3:12-CV-04975-K (USDC, Northern District of Texas, Dallas Division)

Andrea Smith v DePuy Orthopedics, et al., District Court of Tulsa County, Oklahoma, No. CJ-2011-05804

Alysia Ogburn-Sisneros, as personal representative of the estate of Billy Ogburn, Sr., Plaintiff v. Fresenius Medical Care Holdings, Inc.d/b/a Fresenius Medical Care North America, Inc, Fresenius USA, Inc., Fresenius USA Manufacturing, Inc., Fresnius USA Marketing, Inc., and Fresenius USA Sales, Inc., Defendants, Commonwealth of Massachusetts, Superior Court Department, Civil Action No. 13-5050

Center City Periodontists, P.C., et al. v. Dentsply International, Inc., Eastern District of Pennsylvania, Civil Action No. 10-00744.

APPENDIX C: Materials Reviewed and Public Sources of References

Public Sources of References to Food and Drug Laws, FDA Regulations, FDA Guidance, FDA Policy and Procedures, and Definitions

Federal Food, Drug, and Cosmetic Act:
http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/default.htm

21 Code of Federal Regulations:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

FDA Guidance and Policies: www.fda.gov

Merriam-Webster Online Dictionary

Global Harmonization Task Force web site, www.ghtf.org

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